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DHEA in Hair and Glucose Control in African-American Adults

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DHEA in Hair and Glucose Control in African-American Adults

by

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Abstract

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The relationship between dehydroepiandrosterone (DHEA) and glucose control is unclear. Hair DHEA analysis, which allows the assessment of long-term integrated hormone levels, may provide an advantage over previous DHEA measures and bring clarity to the association between DHEA and glucose control. We used the analysis of DHEA in hair to examine associations of long-term DHEA levels with prevalence of Type 2 Diabetes Mellitus (T2DM) and elevated glycated hemoglobin (HbA_{1C}) in a group of African-American adults. Participants included 69 community-dwelling African-American adults (aged 21–84 years; 84% female). The first 3 cm of scalp-near hair were analyzed for DHEA concentration using enzyme-linked immunoassay analysis (ELISA). HbA_{1C} was assessed and dichotomized into T2DM ($HbA_{1C} \geq 6.5\%$) or not and Elevated HbA_{1C} ($\geq 5.7\%$) or not, based on National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) criteria. In logistic regression analyses, DHEA concentrations inversely predicted T2DM and Elevated HbA_{1C} statuses (separately), independent of age, sex, depressive symptoms, and minutes of exercise per week. Long-term DHEA secretion, as assessed in scalp hair, inversely predicted T2DM and elevated HbA_{1C} statuses in African-American adults. Scalp hair may be a useful tool for future work involving DHEA and metabolic function.

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EXPANDED LITERATURE REVIEW

Type 2 Diabetes Mellitus (T2DM) afflicts African Americans at a particularly high rate (1), with 13.2% of African-American adults currently having the disease, compared to 7.6% of non-Hispanic whites and 12.8% of Hispanics. The reasons for this disparity are largely unknown, though levels of certain hormones may be a factor. In particular, African Americans have low concentrations of the androgen hormone dehydroepiandrosterone (DHEA) (2,3), low levels of which have been implicated in T2DM. Controlling for body mass index (BMI), waist-to-hip ratio (WHR) and insulin resistance, African-American women ages 20-60 have DHEA levels significantly lower than Caucasian women, though DHEAS levels in Caucasian women decline more rapidly (2). In a similar study, there was an age by race interaction such that DHEAS levels declined with age at study entry in African-American women ages 35-47, but remained constant in Caucasian women (4). Thus, there is still uncertainty over how DHEA levels in women vary by race and age. In men, the relationship is fairly consistent that African-American men have lower DHEA than Caucasian men (3).

DHEA sulfate (DHEAS) is the most abundantly circulating steroid hormone in humans (5). It is generated in the liver and adrenal gland from DHEA via DHEA sulfotransferase, and acts as a reservoir to the more biologically active DHEA. Only desulfated DHEA is biologically active and available for conversion to downstream sex hormones (6). DHEA circulates in blood at a concentration of 0.01 to 0.02 μM, while DHEAS is quite higher, at 5 to 7 μM (7). DHEAS has relatively longer half-life in the human circulation (less than 10 h) and a slight – yet significant - diurnal variation (about

20%). On the other hand, DHEA's circadian variation is approximately 300% and its half-life is about 30 min (7).

DHEA/S levels peak around age 20-24, and after the second decade of life, decline at approximately 20% per decade (8). Men generally have higher levels than women throughout adulthood, though concentrations become similar near age 70.

Because DHEA decreases steadily with age, it is hypothesized to play a role in many aging-related health complications. However, because it does not have a singular target tissue on which it acts (9), its specific role in the body has been under investigation for some time. DHEA is a neuroactive steroid, playing a role in mental health (7). Low levels are associated with depressive symptoms (10) and schizophrenia, but not bipolar disorder (11).

Low DHEA levels have been implicated in cardiovascular disease and related risk factors. In old age, DHEAS decline is associated with prevalent cardiovascular disease (12). DHEA is also linked with obesity and abdominal adiposity (13), as high levels serve a protective role. In fact, DHEA appears to exert a particularly strong influence on adipose tissue, where concentrations are four to ten times higher than in circulation (14). One such role of DHEA in adipose tissue is increasing insulin sensitivity and enhancing glucose uptake (15). Because of this type of action, DHEA levels have specifically been linked to T2DM and glucose control.

Numerous human studies have shown mixed results examining associations of endogenous DHEA levels with a wide range of glucose metabolism indicators. DHEA is inversely associated with insulin resistance (16, 17), hyperglycemia (18), and T2DM risk

(19). In diabetic patients with hyperinsulinemia, DHEA and DHEAS are chronically depressed compared to nonhyperinsulinemic diabetics and those without diabetes (20). Other research shows a positive association (21, 22) and no association between DHEA and T2DM (23). In cross-sectional studies, DHEA is associated with impaired fasting glucose but not diabetes (24).

DHEA supplementation improves glucose control in diabetic mice (25), and decreases insulin resistance in obese rats (26). While these findings support positive effects of DHEA on glucose metabolism, it must be considered that these animals produce extremely low levels of DHEA, and thus may respond differently to elevated levels than humans.

In humans, the influence of DHEA supplementation on glucose metabolism has also yielded conflicting results. Studies find positive effects of DHEA on glucose tolerance (27), insulin action (28) and hyperglycemia-induced oxidative imbalance (29). Others show no impact of DHEA supplementation in adults for improving contributors of T2DM onset, including insulin sensitivity (30, 31), glycemic metabolism (32), and insulin action (33).

The inconsistent findings surrounding the DHEA-glucose metabolism relationship may be due - at least in part - to methodological challenges inherent in current DHEA assessment techniques. DHEA/DHEAS is primarily measured in blood and saliva, and thus subject to within-person fluctuations. DHEAS, more stable than DHEA throughout the day, still shows significant diurnal variation in serum (34) and saliva (35). These relationships have been shown in Caucasian and Asian adults, but no literature on diurnal

variation in those of African descent exists. The diurnal variation in salivary DHEAS differs by age (36), as older adults have lower and more stable slopes throughout the day. Taken together, these findings could imply that accurate DHEAS measurement would require multiple sample collections per day from each subject, potentially on multiple days. This is demanding of time and resources.

Besides the within-person variability described above, comparing acutely circulating DHEA levels with chronic measures of glucose control like HbA_{1C} (37) may contribute to varying results. The persistent, long-term elevation or suppression of hormones is more likely to influence chronic glucose control than acute fluctuations captured by blood or saliva, as seen in cortisol and blood glucose/HbA_{1C} (38, 39).

Recently, methodological advancements have been made in the detection of hormones in scalp hair. Initially foreseen as a way to detect exogenous androgen steroids in doping-related research (40), hair analyses for endogenous hormones, particularly glucocorticoids, have been widely applied in psychiatric and psychological research (41). Taking advantage of the continuous incorporation of hormones into growing hair, hair analyses are assumed to provide an easily obtainable record of hormone levels integrated over several months.

An important source of variability in hair steroid concentrations that has not been well-investigated is race/ethnicity. Hair grows at different rates based on ethnicity, and nearly all hair steroid studies to date have been done in Caucasians (42). Hair in those of African descent grows at a rate of 0.8 cm/month (43), compared to 1 cm/month in Caucasians. Cortisol is the primary hormone studied in hair, and only two studies have

been done in African-Americans. One combined racial minority groups (African-Cuban, Afro-Cuban, Asian, Brazilian, Indian, Latino-Hispanic and Pacific Islander) vs. non-minorities (44), which is an inappropriate collapsing given the differences in hair growth rate and density found in these various groups. Another study found differing concentrations by ethnicity, with African-Americans having highest concentrations, compared to Hispanics and Caucasians (45). This study also found differences by hair texture, such that tight, curly hair had the highest concentration of cortisol. No studies have examined hair DHEA levels in an ethnicity other than Caucasians, so it remains to be seen if these ethnic differences in cortisol are similar with other hormones.

Of the studies that have measured DHEA in scalp hair, there is a general consistency in physiological ranges, which have been established since 1999 (40). Ranges have been between 0.5-10.6 pg/mg (40), 8.7-426 pg/mg (46), 5.34-42.28 pg/mg (47), and 1.61-25.26 pg/mg (48) in studies examining DHEA in hair. Of note is that these studies use different methods to analyze the hair samples depending on the lab processing the samples. Some investigators use enzyme-linked immunoassay analysis (ELISA), with others employing mass spectrometry (49). The body of evidence encompassing hair DHEA analyses is not yet large enough to determine if one method provides superior results.

There have been advances made on other fronts, however. Recently hair DHEA analysis has demonstrated excellent test-retest reliability, as established with time 1 and time 2 values correlating at $r = 0.81$, $P<.05$ for samples taken one day apart (41). In the same study, however, hair DHEA did not correlate with serum DHEAS at time 1 (r =

0.44, $P = 0.14$) or time 2 ($r = 0.37$, $P = 0.21$). This discrepancy is reasonable, however. DHEAS does not necessarily represent the level of bioactive DHEA in the circulation. As mentioned above, DHEAS levels are at least 200 times greater than DHEA levels, and the interconversion does not happen at a constant rate. It would be nearly impossible, then, to know exactly how much of one hormone is present given the value of the other. Because hair analysis assesses the biologically active DHEA rather than DHEAS, it likely captures a truer picture of the hormone's influence on the body.

Hair analyses may thus prove useful in endocrine and metabolic research, and especially as a measure aligned with the stability and time frame captured by HbA_{1C}. Cortisol (a functional antagonist of DHEA) assessed in hair demonstrates the advantage of this temporal alignment, corresponding as expected with HbA_{1C} but not fasting blood glucose, which is measures acutely circulating glucose (39). Besides the benefits of this alignment with a key health indicator, the actual collection of hair samples offers many practical clinical benefits. Hormone concentrations in hair are extremely stable over many years, and can be stored at room temperature (50). The hair sample collection process does not require specialized equipment, facilities, or biohazard training. Its noninvasive nature may also be more readily accepted by both patients and participants.

Given the recently-discovered advantages of hair steroid analysis and need for more research investigating the DHEA-T2DM relationship, analyzing DHEA concentrations in hair in conjunction with glucose control could provide multiple valuable findings for research and practice alike.

MAIN STUDY

Chapter 1: Introduction

Type 2 Diabetes Mellitus (T2DM) afflicts African Americans at a particularly high rate (1), and the reasons for this disparity are largely unknown. Compared to Caucasians, African Americans have low levels of the androgen hormone dehydroepiandrosterone (DHEA) (2,3), which have been implicated in T2DM. The role of DHEA in glucose metabolism is well studied but unclear, possibly due to methodological challenges in DHEA measurement. Using a novel method of DHEA assessment, this study finds that low levels of DHEA in scalp hair predict elevated risk of T2DM and elevated HbA_{1C} in African-American adults.

DHEA [and its conjugate, DHEA-sulfate (DHEAS)] is the most abundantly circulating steroid hormone in humans (4), and has been of increasing interest to health researchers. Peaking near age 20 and decreasing steadily with age, DHEA is hypothesized to play a role in many aging-related health complications. Given its anti-glucocorticoid properties such as increasing insulin sensitivity and enhancing glucose uptake in adipose tissue (5), declining DHEA levels have specifically been linked to T2DM and glucose control.

DHEA supplementation improves glucose control in diabetic mice (6), and decreases insulin resistance in obese rats (7). While these findings support positive effects of DHEA on glucose metabolism, it must be considered that these animals produce extremely low levels of DHEA, and thus may respond differently to elevated levels than humans.

Numerous human studies have shown mixed results examining associations of endogenous DHEA levels with a wide range of glucose metabolism indicators. DHEA is inversely associated with insulin resistance (8,9), hyperglycemia (10), and T2DM risk (11). In diabetic patients with hyperinsulinemia, DHEA and DHEAS are chronically depressed compared to nonhyperinsulinemic diabetics and those without diabetes (12). Other research shows a positive association (13,14) and no association between DHEA and T2DM (15).

The influence of DHEA supplementation on glucose metabolism has also yielded conflicting results. Studies find positive effects of DHEA on glucose tolerance (16) and hyperglycemia-induced oxidative imbalance (17). Others show no impact of DHEA supplementation in adults for improving contributors of T2DM onset, including insulin sensitivity (18,19), glycemic metabolism (20), and insulin action (21).

The inconsistent findings surrounding the DHEA-glucose metabolism relationship may be due - at least in part - to methodological challenges inherent in current DHEA assessment techniques. DHEA/DHEAS is primarily measured in blood and saliva, and thus subject to within-person fluctuations. DHEAS, more stable than DHEA throughout the day, still shows significant diurnal variation in serum (22) and saliva (23). Further, the diurnal variation in salivary DHEAS differs by age (24). Accurate measurement would thus require multiple sample collections per day from each subject, demanding time and resources.

Besides within-person variability, comparing acute DHEA levels, which is much like a snap shot, with chronic measures of glucose control like HbA_{1C} (25) may contribute

to varying results. The persistent, long-term elevation or suppression of hormones is more likely to influence chronic glucose control than acute fluctuations that are captured by blood or saliva (26).

Recently, methodological advancements have been made in the detection of hormones in scalp hair. Initially foreseen as a way to detect exogenous androgen steroids in doping-related research (27), hair analyses for endogenous hormones, particularly glucocorticoids, have been widely applied in psychiatric and psychological research (28). Taking advantage of the continuous incorporation of hormones into growing hair, hair analyses are assumed to provide an easily obtainable record of hormone levels integrated over several months.

Physiological ranges of DHEA in hair have been established for some time (29), and this method has recently demonstrated excellent test-retest reliability (30). Hair analyses may thus prove useful in endocrine and metabolic research as a measure aligned with the stability and time frame captured by HbA_{1C}. Cortisol (a functional antagonist of DHEA) assessed in hair demonstrates the advantage of this temporal alignment, corresponding as expected with HbA_{1C} but not fasting blood glucose (31).

The purpose of this study was to examine the relationship between DHEA assessed in scalp hair and glucose control in African American adults. Using two thresholds for diabetic ($HbA_{1C} \geq 6.5\%$) and elevated HbA_{1C} ($\geq 5.7\%$) (National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)) (32), it is hypothesized that levels of DHEA in scalp hair will inversely predict prevalence of T2DM and elevated HbA_{1C}.

Chapter 2: Materials and Methods

PARTICIPANTS

Participants were 69 community-dwelling African-American adults who partook in a voluntary research study (84% female; mean age 54.88 years, range 21–84 years). Participants were recruited through word of mouth, and through flyers posted at churches and neighborhood establishments, and on the online University research study announcement board. Exclusion criteria were baldness or shaved head, pregnant or lactating, and prior psychotic disorder diagnosis. In pregnancy, DHEA levels are consistently abnormal (33). In psychotic disorders, DHEA levels are elevated above levels found in normal mental status, and even those with mood disorders (34). Two potential participants were excluded based on these criteria. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of the sponsoring university.

ASSESSMENT OF DEPRESSIVE SYMPTOMS, EXERCISE, AND HAIR-RELATED PARAMETERS

Depression generally impacts both DHEA (35) and glucose control (36), and was thus included as a control variable. Depressive symptoms were assessed by the Patient Health Questionnaire 9 (PHQ-9) (37). Sample items, stemmed by "Over the last three months, how often have you been bothered by any of the following problems?", included "little interest or pleasure in doing things" and "feeling bad about yourself – or that you are a failure or have let your family down". Responses ranged from *0 = not at all*, to *3 = every day*. The PHQ-9 had good internal consistency ($\alpha = .85$).

Exercise is known to influence DHEA levels (38) and glucose control (39), and was also included as a control variable. Exercise was assessed by the single item: "Thinking about the past three months, how many minutes of exercise did you usually perform each week?". The assessment of hair related characteristics included the number of hair washes per week (0-7) and the use of hair treatments during the past three months. Participants answered yes or no to each of the following: coloration, permanent wave, or hair straightening. Responses are reported as yes if participants answered yes to any of the three treatments.

GLYCATED HEMOGLOBIN AND T2DM AND ELEVATED HbA_{1C} DIAGNOSIS

Evening blood samples for the measurement of glycated hemoglobin (HbA_{1C}) were obtained and analyzed at the University of Texas at Austin Family Wellness Center (Austin, Texas) according to standard laboratory procedures. Specifically, HbA_{1C} was measured enzymatically on a DCA Vantage analyzer (Siemens Medical Solutions Diagnostics, Tarrytown, NY). Two cut-points were used for diagnosis: $HbA_{1C} \geq 6.5\%$ (the diabetic threshold; referred to here as T2DM status), and $HbA_{1C} \geq 5.7\%$ (elevated long-term glucose; referred to here as elevated HbA_{1C}). *Note*: elevated HbA_{1C} ($\geq 5.7\%$) includes all cases at or above the threshold, including those in the T2DM category (rather than creating a "prediabetic" group between 5.7% and 6.5%). This was done to maintain adequate sample size for inferential analyses.

HAIR DHEA ANALYSIS

Hair was cut using thinning shears as close to the scalp as possible at the posterior vertex of the scalp, as previously described (40). The hair samples were taped with

painters tape to aluminum foil for protection and storage until all of a subject's hair samples were available and could be processed and analyzed in the same assay to limit variability within participants. Hair DHEA analysis was conducted at the Behavioral Immunology and Endocrinology Lab at the Anschutz Medical Campus - University of Colorado at Denver.

After the hair segments were measured and the proximal 3 cm from the scalp isolated and cut from the remaining length of the hair strands, samples were placed in a pre-weighed 2 ml cryovial (Wheaton, Millville, NJ, USA) and washed three times in 100% isopropanol and dried as previously described (40). After washing, drying, and re-weighing on a high sensitivity electronic balance, the hair was ground in the same tube using a ball mill (Retsch, Haan, Germany) with one 3/16-inch stainless steel ball bearing. Specially milled aluminum cassettes were designed to hold three of these cryovials. The cassettes containing the cryotubes were submerged in liquid nitrogen for approximately 3 minutes to freeze hair samples rendering them brittle for easier grinding. Samples were ground for 4-5 minutes. The powdered hair (5-20 mg) was extracted at room temperature in the same cryovial in HPLC grade methanol overnight on a side-to-side shaker platform. This process ensures no loss of hair in the processing by confining most steps to the same cryovial. Following methanol extraction, the cryovial was spun for three minutes in a centrifuge at 1700g to pellet the hair and the supernatant was removed, placed into a second microcentrifuge tube, and dried under a stream of nitrogen. The extracts were reconstituted with assay diluent based on hair weight. DHEA levels were determined using a commercial high sensitivity EIA kit (Salimetrics LLC, State College,

PA, USA) per manufacturer's protocol. Results are reported as pg/ml which takes into account the amount of hair which was extracted. A pooled control of previously ground hair was extracted as above and included on each EIA plate in duplicate for determination of inter-assay coefficients of variation. Inter-assay coefficient of variation (CV) for the control hair pool was 9.2% and intra-assay CV was 2.8%.

STATISTICAL ANALYSIS

Cleaning of the dataset resulted in exclusion of three cases based on incomplete survey data, for a final data set of 69 participants for analysis. DHEA and HbA_{1c} were not normally distributed, so an analytic approach using nonparametric statistical tests similar to other hair steroid and metabolic research (41) was employed. Spearman's correlation was used to assess associations among variables, and the Mann-Whitney U Test examined sex differences in HbA_{1c} and DHEA.

A three-part analytic strategy was used for the main analyses. First, a logistic regression approach was used to examine the predictive value of DHEA levels for the presence of T2DM and Elevated HbA_{1C} (separately). DHEA data were first entered into these analyses as a continuous variable, excluding two DHEA values > 3 standard deviations (SDs) from the mean due to this test being sensitive to outliers (sample size for logistic regression = 67). Analyses were run in 2 blocks, extending a simple logistic regression model (model 1) with adjustments for age, sex, depressive symptoms and minutes of exercise per week (model 2). Second, using the final adjusted regression models, predicted probabilities of T2DM and elevated HbA_{1C} were calculated based on the DHEA regression coefficient while holding all other covariates at their means. Third,

using the final adjusted regression models for T2DM and elevated HbA_{1C}, odds ratios were calculated for DHEA tertiles. The first and second tertiles were contrasted with the third tertile as the reference category. All analyses were performed using SPSS, version 22 (IBM, Chicago, Illinois).

Chapter 3: Results

Table 1 shows the descriptive characteristics of the study sample. HbA_{1C} was positively associated with age (ϱ = .44, P < .01), and females had higher HbA_{1c} than males (U = 177, P = .018). DHEA was unrelated to sex (U = 233, P = n.s.). Surprisingly, depressive symptoms and minutes of exercise were unrelated to HbA_{1C} (both P = n.s.). DHEA increased with minutes of exercise per week (ϱ = .33, P < .01), but was unrelated to depressive symptoms (P = n.s.). DHEA was unrelated to number of hair washes per week and use of hair treatments (both P = n.s.).

PREDICTING T2DM PREVALENCE AND ELEVATED HbA_{1C} FROM DHEA

Overall, 36.2% of participants were considered to have T2DM based on the HbA_{1C} threshold. An additional 24.7% had elevated HbA_{1C}. Table 2 shows the logistic regression model predicting T2DM status and elevated HbA_{1C} (separately) based on DHEA levels entered as a continuous variable. DHEA was a significant predictor of Elevated HbA_{1C} (OR = .92, P = .022) but not T2DM status in model 1 (OR = .93, P = n.s.). In the final model, which included adjustments for age, sex, depressive symptoms and minutes of exercise per week (model 2), DHEA significantly inversely predicted both T2DM (OR = .89, P = .043) and elevated HbA_{1C} (OR = .89, P = .043). Figure 1 shows the predicted probabilities and 1 standard error confidence intervals of T2DM and Elevated HbA_{1C} status based on DHEA while holding all other covariates at their means. DHEA coefficients for model 2 T2DM and Elevated HbA_{1C} are -0.118 and -0.122, respectively.

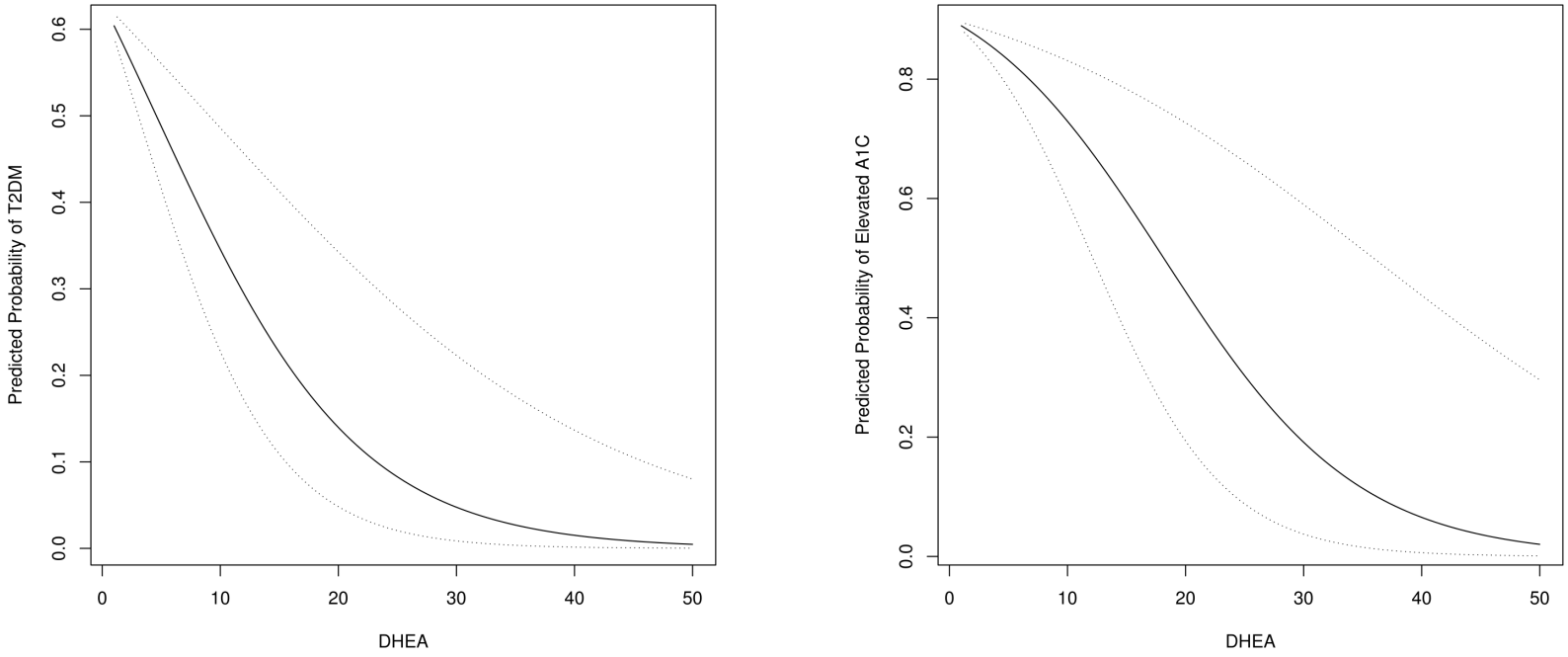
When analyzing DHEA as a categorical variable, we did not observe differences in T2DM (1 vs. 3 OR = 3.46, *P* = n.s.; 2 vs. 3 OR = 1.86, *P* = n.s.) and Elevated HbA_{1C} (1 vs. 3 OR = 1.94, *P* = n.s.; 2 vs. 3 OR = 2.26, *P* = n.s.) odds for DHEA tertiles. Figure 2 shows odds ratios of meeting diagnostic criteria for T2DM and elevated HbA_{1C} based on tertiles of DHEA, given the fully adjusted logistic regression model 2. DHEA tertile means were: first tertile: 5.21 pg/ml; second tertile: 10.67 pg/ml; third tertile: 21.84 pg/ml.

Table 1. Descriptive Information of the Study Sample	
	Total Sample (n = 69)
Demographic and lifestyle parameters	
Age, y	54.88 (14.88)
Sex, n female, % female	58, 84
Depressive symptoms, PHQ-9 score	0.78 (0.69)
Exercise, minutes/wk	149.12 (159.89)
HbA_{1C} and Diagnoses	
HbA_{1C}, %	6.48 (1.60)
Elevated HbA_{1C} ($\geq$ 5.7), n, %	42, 60.9
T2DM ($HbA_{1C} \geq 6.5$), n, %	25, 36.2
Hair-related characteristics and hair DHEA	
Hair washes per week	1.81 (1.82)
Hair treatment, n yes, %	32, 46.0
Hair DHEA, pg/ml	15.30 (18.36)
Data are provided as mean (SD) unless otherwise noted	

Table 2. Logistic Regression Results Predicting T2DM Prevalence and Elevated HbA_{1C} Based on DHEA		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)
T2DM based on DHEA		
Continuous	0.93 (0.86-1.01)	0.89* (0.79-1.00)
First Tertile	2.22 (0.63-7.83)	3.46 (0.72-16.69)
Second Tertile	1.42 (0.40-5.07)	1.86 (0.42-8.29)
Third Tertile	1.00 (referent)	1.00 (referent)
Elevated HbA_{1C} based on DHEA		
Continuous	0.92* (0.86-0.99)	0.89* (0.79-1.00)
First Tertile	2.14 (0.75-8.78)	1.94 (0.31-12.13
Second Tertile	1.88 (0.81-9.31)	2.26 (0.38-13.28)
Third Tertile	1.00 (referent)	1.00 (referent)

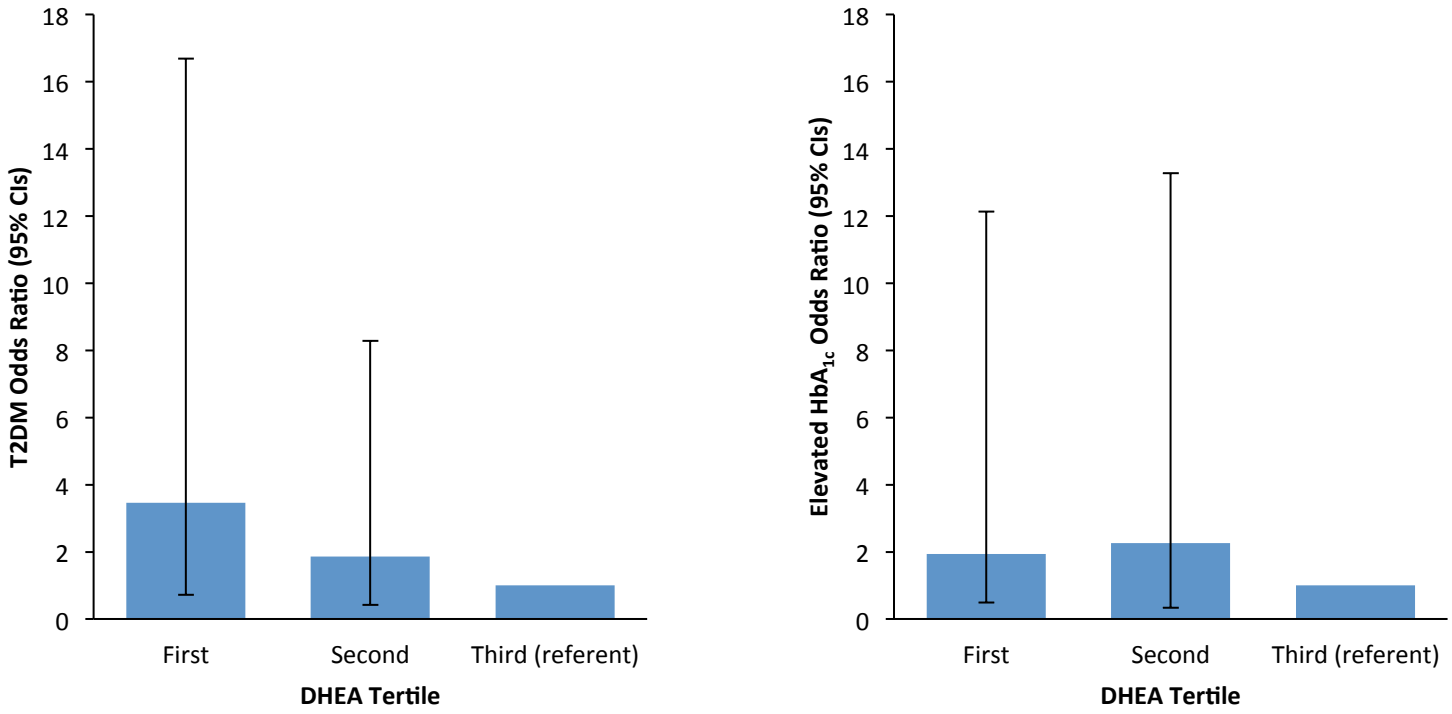
Abbreviations: OR, odds ratio; CI, confidence interval
*, $P < .05$
Model 1 was a simple logistic regression model. Model 2 was adjusted for age, sex, depressive symptoms, and minutes of exercise per week.

Figure 1. Predicted probabilities (1 standard error confidence intervals) for T2DM and Elevated HbA1C based on DHEA.



Figures based on the final adjusted model using DHEA regression coefficient and all covariates held at their means. DHEA values shown in pg/ml

Figure 2. Odds ratios (95% confidence intervals) for T2DM and elevated HbA_{1C} diagnoses based on hair DHEA tertiles.



Data are shown for the fully adjusted model 2, controlling for sex, age, depressive symptoms and minutes of exercise per week.

Chapter 4: Discussion

This study examined associations between long-term DHEA levels, as assessed in scalp hair, and glucose control within an African-American adult sample. The results show an inverse relationship between DHEA levels and glucose control, such that those with lower DHEA concentrations have higher odds ratios of diabetic and elevated HbA_{1C} levels. The evidence linking DHEA and glucose control has been mixed, and these results support previous work demonstrating the anti-glucocorticoid properties of DHEA (8-11).

As a stable marker of hormone levels over several months, hair steroid analysis is becoming more common in psychological and psychiatric research. DHEA in hair has only been assessed in a few prior studies, and the DHEA mean and standard deviation values reported in this study are similar to those reported elsewhere (42). This noteworthy, because this is the first study assessing hair DHEA in a racial group other than Caucasians. It is not yet understood how DHEA levels in hair differ by race, though there may be some racial variation as seen in cortisol (43). Larger studies with more racially diverse samples are needed to better understand whether and how there are racial differences in DHEA hair concentration.

The current study is also the first to show a significant relationship between DHEA in hair and a health indicator. DHEA in hair has been compared with cardiometabolic parameters (blood pressure, cholesterol, blood glucose, etc.) only once (30), with no significant associations found. However, that study only had 13 participants, so its power was quite low. That there was a significant relationship between DHEA and HbA_{1c} in the expected direction in this study is important both

methodologically and practically. From a methods standpoint, it supports the convergent construct validity of hair DHEA analysis.

From a practice standpoint, it helps solidify the relationship between DHEA and glucose control. DHEA not only predicted T2DM prevalence, but also elevated HbA_{1C}, which is a less severe condition that encompasses a larger percent of the population than strictly T2DM. DHEA may thus prove useful as a diagnostic tool for T2DM. Vascular damage can occur in the elevated HbA_{1C} range even before T2DM onset (44), so it is important to identify markers that are related to this condition. Further, as a noninvasive measure, hair analyses offer a method of hormone assessment that does not require specialized collection space, biohazard training, or storage facilities. Hair samples can be stored at room temperature and are stable for years (53). Collection is painless and leaves no noticeable difference in appearance.

It must be considered that this study sample is 85% female, as sex differences are thought to explain some of the conflicting findings surrounding DHEA and glucose control in the literature. We did not observe sex differences in DHEA as expected. This could be due to the small number of men in the study (n = 11). In men, who typically have higher DHEA than women, low DHEA is consistently associated with elevated T2DM risk; in women, this relationship is equivocal (46-48). There is, however a large body of evidence supporting DHEA's protective role against obesity and abdominal adiposity – which is closely linked with glucose control - in women (49). The results of the present clearly support DHEA having a protective effect against T2DM in women, similar to its protective effect on obesity.

As this study was a cross-sectional design, no causal inference into the effects of DHEA on glucose metabolism and vice versa can be made. The interplay between DHEA and glucose is still a chicken-and-egg debate, as DHEA lowers insulin resistance and improves glucose uptake in adipose tissue (32), but is also depressed after the onset of T2DM (50). Experimental studies using DHEA supplementation provide mixed results (51). These must be interpreted carefully, as exogenous DHEA may exert different effects on tissue than DHEA produced in the body (52). Future longitudinal research examining changes in endogenous DHEA over time would be well suited to address this question.

This study was exclusively African-American adults, so generalizations cannot be made to other racial groups or children. This distinction is important because African-American hair grows at a slower rate than Caucasians. Instead of 1 cm per month, it is closer to 0.8 cm per month (53). Thus, if DHEA production were the same across races, African-Americans would have higher concentrations due to the slower growth. Our DHEA concentrations were similar to those found in other recent studies (30,54,55) done in Chinese and European samples, though our sample was considerably older. We would expect the levels to be lower given this older age, but having similar values may reflect the racial difference in hair growth rate. Future studies should assess DHEA in scalp hair in multiple racial groups to better understand these differences, in the hopes of establishing norms and potentially a conversion factor to compare across racial groups.

Depression scores were low with limited variability. The relationship between depression, DHEA and T2DM is complex, as depression is associated with low DHEA

levels (35), and increased in those with T2DM (36). When added to the regression model, depressive symptoms significantly predicted elevated HbA_{1C} but not T2DM, while also moving DHEA from non-significant to significant in the final model. A collinearity check was negative between DHEA and depressive symptoms.

Despite these limitations, this study offers support of low DHEA levels implicated in T2DM and prediabetes risk in African Americans. The use of scalp hair offers promise as a chronic measure of DHEA concentration, especially in relation to glucose control given its temporal alignment with HbA_{1C}. As hair growth rates differ based on race, future research should replicate these findings in other racial groups. Further, DHEA in hair may prove useful in relation to other cardiometabolic markers such as cholesterol, triglycerides, blood pressure, and central adiposity.

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Vita

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