The Association of Cortisol with Prevalent and Incident Type 2 Diabetes in Older Community-Dwelling Adults

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Abstract: *Context:* Previous studies report cross-sectional associations between circulating cortisol levels and type 2 diabetes in older adults; none assessed the association prospectively.

Objective: This study's objective was to examine the association of serum cortisol with prevalent and incident diabetes in community-dwelling older adults.

Methods: Between 1984-87, 885 men and 729 women aged 50 or older had serum fasting morning cortisol measured and an oral glucose tolerance test administered at a baseline research clinic visit and were followed for up to 25 years. Logistic and cox proportional hazards regression models were used to assess cortisol associations with prevalent and incident diabetes.

Results: Median age of participants was 75 years, median body mass index was 25kg/m^2, and median cortisol was 91mg/ml. At baseline, 249 participants had prevalent diabetes; 118 developed diabetes during follow-up. In unadjusted analyses, the odds of prevalent diabetes for the highest cortisol quartile compared to the lowest was 1.95 (95% CI: 1.32, 2.87) and remained significant after adjusting for age, sex and diabetes risk factors (OR: 1.85, 95% CI: 1.21, 2.83); associations were not significant for the second and third quartiles. Serum cortisol was not associated with incident diabetes before or after adjusting for covariates (fully-adjusted HR for highest versus lowest quartile=1.02, 95% CI: 0.58, 1.78).

Conclusions: Results suggest that in older adults, elevated cortisol levels may be a result of diabetes and its complications, rather than a cause. Further studies using cohorts with repeated cortisol measures are needed to confirm the direction of the hypercortisolemia-diabetes link.

Keywords: Cortsiol, type 2 diabetes, prevalent cases, incident cases.

1. INTRODUCTION

Type 2 diabetes usually develops later in life and is a major public health problem affecting over 9% of the U.S. population in 2012 [1]. Diabetes increases the risk of heart disease and stroke, and is the seventh leading cause of death in the U.S. [1]. The estimated prevalence of diabetes in adults aged 65 and older is 26% and the rate of new cases in 2012 was 12 per 1000 persons [1]. Consequently, better understanding of risk factors for diabetes in elders is a major public health goal.

Cortisol is released by the adrenal cortex and increases glucose levels by influencing the metabolism of glycogens, proteins, and lipids [2]. It also increases glucose levels and insulin resistance through its activating effect on glucagon and catecholamines [2]. Overt hypercortisolemia due to Cushing's Syndrome is a well-recognized cause of hyperglycemia [3]. It is also possible that treatment induced hypoglycemia of diabetes patients and co-morbidities may also result in high cortisol levels [4]. Thus, cortisol may play a role in the development of type 2 diabetes or be impacted by the disease progression and treatment.

Several studies have reported an association between elevated cortisol and diabetes in older adults [4-8]. Schorlemmer and colleagues [5] showed that salivary cortisol levels in the highest tertile were associated with 33% greater odds of diabetes in women aged ≥ 65 years, and a hospital based case-control study found that older men and women with diabetes had a 4·8 times greater likelihood of subclinical hypercortisolism compared to those without diabetes [7]. In a patient-based study, urinary free cortisol and post-dexamethasone cortisol levels were significantly higher in diabetic patients compared to obesity-matched patients and normal weight controls [6]. Finally, the Multi-Ethnic Study of Atherosclerosis [4]

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found that women, but not men, with diabetes had significantly higher integrated cortisol levels over the diurnal period. All of these studies were cross-sectional, thus the direction of the cortisol – diabetes association cannot be determined, and whether hypercortisolemia plays a role in the pathophysiology of diabetes is unclear.

The purpose of our study was to examine both the cross-sectional and prospective associations of fasting serum cortisol with diabetes in a large sample of older, community-dwelling men and women who had diabetes assessed by oral glucose tolerance test at baseline and were followed for incident diabetes for up to 25 years. This was assessed in order to evaluate whether elevated cortisol levels are a cause or result of diabetes and its complications.

2. METHODS

2.1. Participants

Between 1972-74, 82% of adult residents of Rancho Bernardo, a predominately Caucasian, middle-class Southern California community, were enrolled in a study of heart disease risk factors, known as the Rancho Bernardo Study of Healthy Aging. These individuals have been followed since with periodic research clinic visits in 1989-1990, 1992-1994; 1997-1999; 1999-2001; 2003-2005; 2007-2008 and yearly mailed surveys. In 1984-87, 2,390 of these individuals aged 50 and older attended a follow-up clinic visit. Of these, 776 were excluded for no cortisol measurement or current use of glucocorticoid medications; the remaining 1614 (885 men and 729 women) form the basis of this analysis. This study was approved by the Human Research Protections Program of the University of California San Diego; all participants gave written informed consent prior to participation.

2.2. Procedures

Blood samples were taken during the 1984-87 clinic visit. Although, the cortisol measurements were completed later in 1992-1994, these samples were used as the baseline cortisol measurements for both the cross-sectional and prospective studies.

During the 1984 to 1987 visit, standardized questionnaires were used to collect information on age, alcohol consumption (drinks per week), smoking status (never/past/current), and family history of diabetes. The Beck Depression Inventory (BDI) was used to assess mood [9]. Weight, height, waist and hip girths were measured with participants wearing light clothing and no shoes. Body mass index (BMI) (kg/m^2) and waist-hip ratio (WHR) were used as estimates of overall and central adiposity, respectively. Blood pressures were measured twice, five minutes apart, in seated participants by a nurse trained in the Hypertension Detection and Follow-Up Program protocol [10]; heart rate (beats per minute) was also recorded. Medication use was validated with pills and containers brought to the clinic for that purpose.

A 75-g oral glucose tolerance test was administered between 0730 and 1100 h after a requested 12-h fast; clock time of initial blood collection was recorded. Blood samples were drawn by venipuncture at 0 and 2 h, and serum and plasma were separated and frozen at −70°C. Fasting and 2hr post-challenge plasma glucose was measured by the glucose oxidase method; insulin concentrations were determined by radioimmunoassay in a diabetes research laboratory. Fasting serum cortisol was measured by direct radioimmunoassay (RIA) in 1992-94 at the University of California San Diego Reproductive Medicine endocrine laboratory using first-thawed samples. The assay sensitivity was 17nmol/L and the intra- and interassay coefficients of variation were 5.4% and 10.5%, respectively.

2.3. Diabetes Assessment

Prevalent diabetes was defined by self-report of physician diagnosis, fasting plasma glucose ≥126mg/dL, 2-h post-challenge glucose ≥200mg/dL, or use of diabetes medications. Incident diabetes, defined as presence of any of the prevalent diabetes criteria, was assessed at seven subsequent follow-up clinic visits and by six mailed questionnaires over a maximum 25-year follow-up period. The exception was post-challenge glucose, which was only available at one follow-up visit a median of 8 years after the baseline visit. Of 1247 participants without diabetes at baseline, a total of 997 participants (451 women and 546 men) were followed for incident diabetes. A total of 250 participants died, moved or were lost to follow-up.

2.4. Statistical Analysis

Unadjusted comparisons of covariates for participants by diabetes status were performed using ANOVA for continuous variables and chi-squared tests for categorical variables. Tukey-Kramer tests were used for post-hoc comparisons. The association of cortisol with diabetes was assessed by logistic regression for prevalent diabetes and by Cox proportional hazards regressions for incident diabetes.

Participants with prevalent diabetes were excluded from the incident diabetes analyses. Cortisol was modeled as quartiles based on the total study sample for prevalent diabetes and on the follow-up sample for incident diabetes. Four successive regression models were evaluated: the first was unadjusted, the second adjusted for age and sex, the third added adjustment for lifestyle, and the fourth added adjustment for adiposity and other diabetes risk factors. If two variables were correlated (such as BMI and waist girth) in the model as measured by a variance inflation factor > 10, only one was included in the final analysis. Time of blood draw was included in all multivariate models to minimize the influence of circadian changes in cortisol levels. Models were tested for interactions of cortisol with sex and with age; none were significant (*P*'s > 0.15). All analyses were performed with SAS version 9.3; $P < 0.05$ was considered statistically significant.

Table 1: Comparison of Baseline Characteristics by Diabetes Status

Characteristic	No Diabetes *N* = 1247	Prevalent Diabetes *N* = 249	Incident Diabetes *N* = 118	*P**
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	72.7 ± 9.1	74.7 ± 8.1	66.4 ± 8.9	<0.001
Cortisol (ng/ml)	95.8 ± 33.0	101.4 ± 33.9	86.5 ± 30.6	0.003
Waist girth (cm)	86.4 ± 11.5	89.6 ± 12.1	91.6 ± 12.2	<0.001
BMI (kg/m^2)	24.8 ± 3.4	25.7 ± 4.0	26.7 ± 3.8	<0.001
WHR (Waist/Hip Ratio)	0.86 ± 0.08	0.88 ± 0.08	0.88 ± 0.08	0.003
Triglycerides (mg/dl)	113.5 ± 70.7	152.3 ± 109.8	138.3 ± 86.7	<0.001
HDL cholesterol (mg/dl)	60.4 ± 17.6	55.5 ± 18.5	54.1 ± 17.4	<0.001
Systolic Blood Pressure (mmHg)	140.7 ± 21.5	149.1 ± 21.0	137.6 ± 17.9	<0.001
Diastolic Blood Pressure (mmHg)	76.7 ± 9.3	77.6 ± 10.0	78.5 ± 9.3	0.083
Fasting Glucose (mg/dl)	96.4 ± 10.3	128.0 ± 37.0	103.3 ± 10.9	<0.001
Non-fasting Glucose (mg/dl)	123.3 ± 33.1	239.3 ± 76.0	135.0 ± 35.0	<0.001
Heart Rate (beats/ minute)	62.6 ± 10.1	64.3 ± 11.7	61.4 ± 9.0	0.022
Beck Depression Index	6.0 ± 4.7	6.5 ± 4.4	5.3 ± 3.8	0.057
Time of Blood Draw (clock time) (+/- minutes)	9:09 ± 41	9:07 ± 44	9:07 ± 39	0.94
	N (%)	*N* (%)	*N* (%)	
Sex (Male)	672 (54)	129 (52)	84 (71)	<0.001
Metabolic Syndrome	138 (11)	109 (44)	29 (25)	<0.001
Alcohol (3+ drinks/wk)	679 (54)	113 (45)	61 (52)	0.032
Smoking				0.44
Never	495 (40)	99 (40)	50 (42)	
Past	596 (48)	128 (51)	57 (48)	
Current	156 (13)	22 (9)	11 (9)	
Family history diabetes				
Maternal	88 (7)	37 (15)	13 (11)	<0.001
Paternal	52 (4)	15 (6)	8 (7)	0.37

*p-value for differences across diabetes status groups.

3. RESULTS

Average age at baseline was 71 ± 10 years in men and 74 ± 8 years in women. Cortisol ranged from 12 to 300ng/ml with a mean of 96ng/ml. Overall, 15%, (129 men and 120 women) were classified as having prevalent diabetes at the 1984-87 clinic visit. Of these, 71 (29%) reported a physician diagnosis of diabetes; the remaining prevalent cases were based only on glucose measures and/or use of diabetes medications. Of prevalent diabetes cases, 28 were based on elevated fasting glucose alone and 107 on elevated post-challenge glucose alone. During up to 25 years of follow-up, there were 118 incident diabetes cases (84 men and 34 women); 10 were based on physician diagnosis; the remaining cases were based on glucose measurements and/or use of diabetes medications. Median time to incident diabetes was 14 years (range 3 to 24 years).

Table **1** shows comparisons of participant characteristics by diabetes status: no diabetes, prevalent diabetes, and incident diabetes. Compared to those with no diabetes, those with prevalent or incident diabetes had significantly higher waist circumference, BMI, WHR, triglycerides, and fasting plasma glucose, a higher prevalence of metabolic syndrome and maternal diabetes history, and lower HDL cholesterol; heart rate tended to be highest in those with prevalent diabetes and lowest in those with incident diabetes. Cortisol levels differed significantly by diabetes status with higher levels among participants with prevalent diabetes compared to those with no diabetes, and lower levels among those with incident diabetes (P = 0.0003).

Table **2** presents the odds of prevalent diabetes by cortisol quartile with the lowest quartile as the reference. Cortisol levels in the highest quartile were associated with significantly higher odds of prevalent diabetes compared to the lowest quartile in the unadjusted model (OR: 1.95, 95% CI: 1.32, 2.87); this association remained significant after sequential adjustment for sex, age, lifestyle and diabetes risk factors. Cortisol quartiles 2 and 3 were not significantly associated with prevalent diabetes in any model. In sensitivity analyses, adding fasting plasma glucose or post-challenge glucose to model 4 eliminated the

Table 2: Odds Ratios (OR) for Prevalent Diabetes (*n*=249 Cases, 1365 Non-Cases) by Quartile of Cortisol

Cortisol Quartile (ng/ml)	No. Cases	Model 1 OR [95% CI]	Model 2 OR [95% CI]	Model 3 OR [95% CI]	Model 4 OR [95% CI]
Q1 (12-74)	50	1.0 [ref]	1.0 [ref]	1.0 [ref]	1.0 [ref]
Q2 (74-92)	61	1.25 [0.83, 1.86]	1.11 [0.74, 1.67]	1.14 [0.76, 1.72]	1.18 [0.77, 1.80]
Q3 (93-113)	53	1.14 [0.75, 1.73]	1.00 [0.65, 1.52]	1.00 [0.65, 1.54]	1.02 [0.65, 1.58]
Q4 (114-300)	85	1.95 [1.32, 2.87]	1.68 [1.13, 2.51]	1.71 [1.14, 2.56]	1.85 [1.21, 2.83]
P		0.003	0.018	0.016	0.007

Model 1, unadjusted.

Model 2, adjusted for sex, age, and time of blood draw.

Model 3, Model 2 + heart rate (measure of fitness), alcohol, smoking status.

Model 4, Model 3 + BMI, HDL, triglycerides, SBP.

Table 3: Hazards Ratios (HR) for Incident Diabetes (*n*=118 Cases, 879 Non-Cases) by Quartile of Cortisol

Cortisol Quartile (ng/ml)	No. Cases	Model 1 HR [95% CI]	Model 2 HR [95% CI]	Model 3 HR [95% CI]	Model 4 HR [95% CI]
Q1 (12-70)	39	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
Q2 (71-88)	24	0.93 [0.56, 1.53]	0.74 [0.44, 1.23]	0.73 [0.44, 1.21]	0.74 [0.44, 1.25]
Q3 (89-109)	34	1.48 [0.90, 2.41]	1.25 [0.75, 2.09]	1.25 [0.75, 2.09]	1.32 [0.78, 2.20]
Q4 (110-259)	21	1.13 [0.68, 1.89]	0.95 [0.56, 1.62]	0.92 [0.53, 1.59]	1.02 [0.58, 1.78]
P		0.30	0.74	0.81	0.54

Model 1, unadjusted.

Model 2, adjusted for sex, age, and time of blood draw.

Model 3, Model 2 + heart rate (measure of fitness), alcohol, smoking status.

Model 4, Model 3 + BMI, HDL, triglycerides, SBP.

significant association for cortisol quartile 4 [OR: 1.34 (95% CI: 0.78, 2.29) and 0.95 (95% CI: 0.50, 1.84), respectively].

As shown in Table **3**, for those without diabetes at baseline, there was no significant association of baseline cortisol quartile with incident diabetes during follow-up either before or after adjusting for covariates. In Model 4, the hazards ratios for incident diabetes were 2·0 (95% CI 1.6-2.7) for a 10-year increase in age, 1.2 (95% CI 1.1-1.3) for a 10mm Hg increase in SBP, and 1.3 (95% CI 1.1-1.6) for a SD (3.5kg/m^2) increase in BMI, demonstrating sufficient power to identify classic diabetes risk factors. Cortisol associations with incident diabetes remained insignificant when the highest, rather than the lowest, cortisol quartile was chosen as the reference category and when cortisol was modeled as a continuous variable (data not shown).

4. DISCUSSION

To our knowledge, this is the first study to report the cortisol-diabetes association with both prevalent and incident diabetes in a community-dwelling, non-clinic-based population. Cortisol levels in the highest quartile (median=132ng/ml for this sample) were associated with nearly 2-fold higher likelihood of prevalent diabetes independent of age, sex, lifestyle and other diabetes risk factors. However, we did not find a significant association between circulating cortisol concentrations and development of diabetes in this elderly population during a median 14-year follow-up.

The association of hypercortisolemia with prevalent diabetes in the present study did not differ by sex. This contrasts with the MESA study of older adults in which salivary cortisol levels collected from time of waking to bedtime were elevated in women, but not men, with diabetes compared to those without diabetes [4]. The Longitudinal Aging Study Amsterdam [5] also found sex-specific associations; however, they varied by the source and timing of the cortisol measurement. Morning serum cortisol was higher in men with diabetes and evening salivary cortisol was higher in women with diabetes; nonetheless both sexes exhibited some degree of hypercortisolemia in conjunction with diabetes. In a case-control study of hospitalized men and women, aged 30 to 80 years, those with diabetes had 4.8 times greater odds of subclinical hypercortisolism, based on multiple criteria, independent of sex, age and the reason for hospitalization [7]. Thus, hypercortisolemia has been a consistent characteristic of individuals with diabetes in several studies.

Champaneri *et al.* (4) hypothesized that higher cortisol levels in patients with diabetes may be a result of hypoglycemia induced by diabetes treatment as well as diabetes co-morbidities. In accord with this idea, two studies of patient populations [11, 12] found that the degree of hypothalamic-pituitary-adrenal (HPA) hyperactivity was highest in diabetes patients with chronic complications. In our study only a third of prevalent cases had physician-diagnosed diabetes or were receiving insulin or diabetes medications and cortisol levels did not differ by treatment status, suggesting that cortisol levels are significantly elevated even in undiagnosed and untreated diabetics. Hypercortisolemia may become more pronounced as diabetes disease progresses for a variety of reasons, including direct or stress-related effects of diabetes complications [4, 7, 11]. Importantly, our findings in a non-clinic based population suggest that dysregulation of the HPA axis may be an early feature of diabetes. Whether this is due to stimulation of adrenal secretory activity by hyperinsulinemia [13] or other factors requires further study.

Our study did not find a prospective association of cortisol and incident diabetes, although an association between elevated cortisol and diabetes is biologically plausible. Cortisol alters the metabolism of glycogen, protein, and lipid metabolism which increases glucose in the blood stream [2]. Additionally, cortisol increases insulin resistance and glucose by activating glucagon and catecholamines [2]. Therefore, it is conceivable that exposure to high cortisol levels over long periods of time may be associated with the development of type 2 diabetes. However, it is not known if the increase of cortisol occurs shortly before the development of diabetes or a long time before the diagnosis of diabetes. We were not able to determine this in our study because we did not measure cortisol beyond baseline, a limitation of our findings.

Strengths of this study are the relatively large sample size and the prospective design with participants followed for up to 25 years. Importantly, we were able to identify prevalent cases based on oral glucose tolerance measurements. Early studies in the Rancho Bernardo cohort showed that more than half of type 2 diabetes cases would be missed if post-challenge hyperglycemia was not assessed, particularly for older women [14, 15]. Only one follow-up diabetes assessment included a post-challenge

glucose measurement, consequently, we may not have captured all incident cases; nonetheless we found the expected predictive associations for age, BMI and systolic blood pressure. The diagnosis of diabetes was also based partially on self-report; however, the upper-middle class socioeconomic status and high educational level of this cohort means that self-reported medical history is likely to be reliable. Confirmation of self-reported coronary heart disease, cancer and diabetes by record review has always exceeded 85% [16].

We only had a single measurement of cortisol, which may have limited associations, but is unlikely to have caused them. All blood samples were drawn fasting in the early morning, and we adjusted for time of specimen collection; both should reduce bias related to the diurnal variation of cortisol levels. Another limitation is the homogenous nature of the Rancho Bernardo cohort, which may reduce generalizability to the general population, but is a strength to the extent that it reduces confounding by race, socioeconomic status, and access to health care. In addition, previously published reports show that compared with national, representative samples of persons their age, those in the Rancho Bernardo cohort are on average somewhat leaner [14], but are no more or less likely to have been cigarette smokers [17], and to have similar levels of alcohol consumption, systolic blood pressure, diabetes, impaired glucose tolerance, and plasma cholesterol [18-23].

CONCLUSION

In conclusion, elevated cortisol levels were significantly associated with prevalent diabetes, but not incident diabetes, in this cohort of older, community-dwelling men and women. This suggests that hypercortisolemia in older adults with diabetes may be a result of diabetes and its complications, rather than contributing to the pathogenesis of diabetes. Future studies should focus on assessing the cortisol-diabetes association prospectively using multiple measures of cortisol to confirm the direction and timing of the hypercortisolemia-diabetes link.

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