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EFFICACY OF DUTASTERIDE IN MEN WITH LOW PROSTATE VOLUME IN THE REDUCTION BY DUTASTERIDE OF PROSTATE CANCER EVENTS (REDUCE) STUDY

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INTRODUCTION AND OBJECTIVES: In the REDUCE study, dutasteride (DUT) compared with placebo (PBO) reduced the risk of incident prostate cancer by 23% and improved outcomes related to benign prostatic hyperplasia (BPH) in men with increased risk of PCa. Because previous DUT studies only enrolled men with enlarged prostates, and because prostate cancer has been reported to be more prevalent in men with small prostates, we now report the effect of DUT on PCa and BPH endpoints in men with low baseline prostate volume (PV) in REDUCE.

METHODS: The REDUCE study was an international, randomized, double-blind, PBO-controlled study. Men received DUT (0.5 mg daily) or PBO for 4 yrs. Eligible subjects included men 50–75 yrs, with prostate specific antigen (PSA) level 2.5–10 ng/ml and a single negative prostate biopsy (6–12 cores) within 6 months of enrollment. International Prostate Symptom Score (IPSS) and serum PSA levels were measured every 6 months. PV was measured by ultrasonography at randomization and at 2 and 4 yrs. Biopsies (10 cores) were performed at 2 and 4 yrs or when clinically indicated. Two-sided P values of ≤ 0.01 indicated statistical significance in the assessment of the superiority of DUT over PBO. In the present analysis we investigate outcomes related to PCa and BPH in the subgroup of men with a baseline PV <30 cc.

RESULTS: Within the REDUCE population, 774 men from the DUT group and 807 men from the PBO group had a PV <30 cc. Baseline characteristics were similar between treatment groups (Table). 225 cases of PCa were detected in the PBO group and 165 cases in the DUT group ($p=0.0035$), representing an incidence of 27.9% vs. 21.3%, respectively. Fewer men in the DUT group had BPH-related surgery ($p=0.0014$) and acute urinary retention (AUR) ($p=0.00540$) than in the PBO group. IPSS scores were lower than baseline at Month 48 in the DUT group, but higher than baseline in the PBO group ($p<0.0001$). The change in PV from baseline to Month 48 was significantly different between treatment groups ($p<0.0001$), however, the minimal decrease in the DUT group and large increase in the PBO group may imply a regression of the mean from baseline to follow-up PV measurements.

CONCLUSIONS: In men with low PV, DUT lowered the overall incidence of PCa, led to greater improvements in IPSS scores and improved BPH-related outcomes over the 4-yr study period.

Table. Baseline characteristics and PCa and BPH results in men with low prostate volume

	Dutasteride (n=774)	Placebo (n= 807)
BASELINE CHARACTERISTICS		
Mean age (yr)	61.5	61.6
Mean total PSA (ng/ml)	5.45	5.60
Mean IPSS	7.6	7.6
Mean PV (cc)	23.6	23.5
—	—	—
PROSTATE CANCER RESULTS		
Incidence (%)	165 (21.3)	225 (27.9)
Relative risk reduction (95% CI)	24.1 (8.6, 36.9)	—
—	—	—
BENIGN PROSTATIC HYPERPLASIA RESULTS		
BPH-related surgery: incidence (%)	5 (0.6)	22 (2.7)
BPH-related surgery: relative risk reduction (95% CI)	76.6 (38.3, 91.2)	—
AUR: Incidence (%)	9 (1.2)	26 (3.2)
AUR: relative risk reduction (95% CI)	64.3 (23.8, 83.3)	—
Change in IPSS at Month 48: adjusted mean (SE)	−0.36 (0.186)	1.21 (0.181)
% change in PV at Month 48: adjusted mean (SE)	−0.7 (1.88)	41.4 (2.60)
Use of alpha blocker (%)	74/774 (9.6)	115/807 (14.3)

*Percentages based on biopsied population (placebo n=620; dutasteride n=671). CI=confidence interval; SE=standard error.

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MINIMALLY INVASIVE 16G OPTICAL BIOPSY NEEDLE FOR PROSTATE CANCER DIAGNOSIS

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INTRODUCTION AND OBJECTIVES: Random transrectal prostate biopsies often fail to diagnose prostate cancer (PCa) and to accurately grade and stage this disease. The concentrations of natural fluorophores (*e.g.,* tryptophan) in prostate tissue fluctuate with disease states. Thus, fluorescence spectroscopy could quantify these fluctuations to identify PCa. The objective of this research is to determine the potential clinical utility of an optical biopsy needle to diagnose PCa.

METHODS: An optical biopsy needle with a light sensitive optical probe at the tip of the inner needle was developed to take prostate biopsies using BARD MAGNUM gun while measuring tissue fluorescence with a fluorometer. Optical probe consists of eight 100μm fibers for tissue excitation and a single 200μm fiber to capture fluorescence spectra. We took random biopsy cores from 10 prostates *ex vivo* after measuring emission spectra between 295–550nm from tissue fluorescence for excitation wavelengths between 280–350nm. Each biopsy core was histopathologically classified and correlated with their respective spectra. Prostate biopsies were grouped into benign or malignant based on the histological findings within 1mm length of each core's distal-end. Partial least square analysis of tissue spectra was performed to identify principal components (PCs) as potential classifiers. Using linear support vector machine and leave-one-out cross validation method, selected PCs were tested for their ability to classify benign vs. malignant prostatic tissue.

RESULTS: A total of 104 biopsies, 73 benign and 31 malignant, were studied. *P* values for PC1–PC5 as potential classifiers are shown in Table I. Based on Pearson correlation coefficients, one set of statistically significant ($p<0.05$) but least correlative PCs were identified: PC1–PC3 each at 290 and 330nm, and PC1 & PC2 at 350nm (shown in bold). These PCs provided 83.9% sensitivity, 95.9% specificity, 91.2% positive predictive value, and 93.3% negative predictive value for benign vs. malignant prostatic tissue classification.

CONCLUSIONS: Optical biopsy needle guided by tissue fluorescence can differentiate *ex vivo* benign vs. malignant prostatic tissues. This method could be applied *in vivo* for more precise targeting of PCa lesions, providing more accurate assessment of grade and stage of disease, with the consequent improvement of patient care.

Table I: Principle Components and corresponding p values

Excitation Wavelengths	280nm	290nm	300nm	330nm	340nm	350nm
Principle Components						
PC1	7.82×10^{-6}	5.42×10^{-5}	4.57×10^{-6}	2.08×10^{-4}	1.24×10^{-4}	1.16×10^{-5}
PC2	1.28×10^{-5}	1.45×10^{-5}	2.92×10^{-6}	3.04×10^{-3}	2.40×10^{-3}	2.91×10^{-3}
PC3	6.50×10^{-5}	3.48×10^{-7}	1.38×10^{-3}	0.02	0.09	0.02
PC4	3.11×10^{-3}	9.49×10^{-3}	5.83×10^{-3}	2.59×10^{-4}	8.16×10^{-4}	3.41×10^{-3}
PC5	0.14	0.63	0.04	4.58×10^{-3}	0.05	5.96×10^{-3}

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Stone Disease: Basic Research

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FRACTIONAL CALCIUM ABSORPTION AND HISTORY OF NEPHROLITHIASIS IN OLDER WOMEN IN THE STUDY OF OSTEOPOROTIC FRACTURES

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INTRODUCTION AND OBJECTIVES: Intestinal absorption of calcium is known to play a critical role in hypercalciuric nephrolithiasis, a urinary metabolic defect present in up to 50% of calcium stone formers. A few small studies have used radioactive calcium to examine the association between intestinal calcium absorption and hypercalciuria, but no study has evaluated the association with nephrolithiasis. The purpose of this study was to evaluate the relationship between patient reported history of nephrolithiasis, fractional absorption of calcium, and the effect on bone mineral density (BMD).

METHODS: The Study of Osteoporotic Fractures (SOF) is a cohort of 9704 older women enrolled in 1986 and followed prospectively for more than 20 years. We performed secondary analyses of 7982 women who reported their kidney stone history and then presented in 1992, where 5452 patients (82%) underwent oral radioactive calcium assay (45Ca). We evaluated the relationship between nephrolithiasis, fractional calcium absorption and BMD.

RESULTS: Women with a history of nephrolithiasis had higher BMIs ($p<0.01$), and were less likely to currently use calcium supplements ($p=0.02$). For each 10% increase in fractional calcium absorption, there was a 30% (CI 12–51%, $p<0.001$) increased risk of nephrolithiasis. This risk was more pronounced (51%, CI 3–120%, $p=0.03$) among women that never supplemented calcium. Dietary calcium was not associated with nephrolithiasis. Among women that never used calcium supplements, there was a trend towards lower BMD in stone formers ($p=0.07–0.13$) at all sites except the spine. Women who used calcium supplements had similar BMD, regardless of nephrolithiasis history. After adjusting for age, BMI, health status, calcium supplementation and thiazide diuretic use, each 10% increase in fractional calcium absorption was associated with a 38% (CI 16–66%, $p<0.001$) increased risk of having a history of nephrolithiasis.

CONCLUSIONS: These data provide direct evidence that elevated intestinal calcium absorption is associated with an increased likelihood of historic nephrolithiasis. Women that supplemented calcium were less likely to have a history of nephrolithiasis, and had lower calcium absorption which may have prevented some of the decreased BMD seen in those with a history of nephrolithiasis. Although the mechanism remains to be established, these findings provide further evidence that calcium supplementation reduces the risk of nephrolithiasis; interventions to reduce intestinal calcium absorption may reduce the likelihood of nephrolithiasis.

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TOTAL CALORIC INTAKE MODULATES RISK FOR URINARY STONES IN WOMEN: RESULTS FROM THE WOMEN'S HEALTH INITIATIVE

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INTRODUCTION AND OBJECTIVES: The mechanism underlying the association between obesity and stones remains poorly understood. Our objective was to examine the dietary factors that modulate risk for kidney stones in the obese and overweight.

METHODS: Utilizing data from the Women's Health Initiative Observational Study (a cohort of 93,676 postmenopausal women aged 50-79 enrolled between 1994 and 1998 across 40 clinical sites in the United States), this prospective observational cohort study utilized self report and clinic visit assessment to identify patients with at least one symptomatic episode of kidney stones. Clinic visit data was used to calculate body mass index (BMI) for this cohort. Validated dietary questionnaires measured daily caloric and other diet-related intake. Patients were stratified into categories of BMI. Dietary intake was examined for risk factors modulating risk of stone disease in this population.

RESULTS: For this analysis, 78,551 participants were included who had complete data on diet, BMI, and incidence of symptomatic nephrolithiasis. Within this group, 1,960 (2.5%) patients with a mean age of 63.7 + 7.6 years reported at least one episode of symptomatic stone occurrence. BMI demonstrated the strongest association with increased risk of nephrolithiasis. Overweight (BMI 25.0–29.9) and obesity level I–III (BMI 30.0–34.9, 35.0–39.9, and > 40.0) individuals had unadjusted odds ratios of 1.3 (95% confidence interval 1.1–1.4), 1.8 (95% confidence interval 1.5–2.0), 2.1 (95% confidence interval 1.8–2.5), and 2.4 (95% confidence interval 1.9–2.9) respectively for an episode of symptomatic nephrolithiasis when compared to normal individuals (BMI 18.5–24.9). With univariate analysis, ingesting a higher amount of total calories (>2500 kcal/day) conveyed an increased odds ratio for nephrolithiasis of 1.7 (95% confidence interval 1.4–2.0) when compared to a daily caloric intake of <1500 kcal/day. Adjusted for BMI, this odds ratio remained elevated at 1.5 (95% confidence interval 1.2–1.8) for participants in the highest caloric intake group.

CONCLUSIONS: Among various metabolic variables, obesity was most strongly associated with an increased risk of stone disease, but when adjusted for these variables, total caloric intake conferred an independent increased risk for nephrolithiasis. Regulating the total number of calories ingested daily may play a significant role in risk reduction for stone disease in obese and overweight individuals. To the best of our knowledge, this is a newly identified dietary risk factor for nephrolithiasis.

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