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A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial

Jonathan L Wright^{1,2,3}, Stephen Plymate^{4,6}, Andrea D'Oria-Cameron², Carolyn Bain², Kathy Haugk, Liren Xiao², Daniel W Lin^{1,2,3}, Janet L Stanford^{2,5}, and Anne McTiernan²

¹Department of Urology, University of Washington School of Medicine, Seattle, WA

²Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

³Urology Section, VA Puget Sound Health Care System, Seattle, WA

⁴Department of Medicine, University of Washington School of Medicine, Seattle, WA

⁵Department of Epidemiology, University of Washington School of Public Health, Seattle, WA

⁶Health Services Research & Development and GRECC, VA Puget Sound Health Care System, Seattle, WA

Abstract

Introduction—Obese men have an increased risk of prostate cancer (PCa)-specific mortality. Potential mechanisms include insulin and related proteins. We investigate whether a short-term caloric restriction diet in overweight/obese men with newly diagnosed PCa can lead to measurable changes in patient anthropometrics and insulin-related proteins.

Methods—Overweight and obese PCa patients choosing active surveillance or radical prostatectomy were randomized to a 6-week, caloric-restricted diet or to continue their current diet. Changes from baseline to end of study in anthropometrics, dietary constituents and serum proteins (insulin, c-peptide, IGF-1, adiponectin, IGF-BP3) were compared between the intervention and control groups using a Generalized Estimating Equation model.

Results—Nineteen patients were randomized to the intervention (N=10) or control (N=9) group. Men in the intervention group had a 1.7% (3.7 lbs.) mean decline in weight vs. 1.0% (2.0 lbs.) in controls ($p<0.05$), and a reduced intake of calories, total and saturated fat, protein and starch, (all $p<0.1$ compared to controls). There was a significant difference ($p=0.002$) in mean serum IGFBP-3 between the intervention (+2.8%) and control group (−6.9%). Other biomarkers changed with the diet intervention to a degree similar to previous weight loss studies but were not statistically significant compared with controls.

Conclusion—In this small pilot study, a 6-week caloric restricted diet in men with newly diagnosed PCa produced changes in weight, diet and serum proteins possibly related to prognosis. These results support larger-scale trials testing longer-term weight loss effects on potential PCa progression biomarkers.

Introduction

Epidemiologic studies have consistently associated obesity with an increased risk of prostate cancer (PCa) progression and PCa-specific mortality.(1-5) In a retrospective study of men with organ-confined, margin-negative PCa after radical prostatectomy, the most obese men had a 4-fold increased relative risk of progression after adjusting for Gleason grade.(6) A small study in men with PCa showed that a short term low glycemic intervention can lead to changes in gene expression with mechanisms associated with cancer aggressiveness and proliferation.(7) Considering the increasing prevalence of both obesity (8) and PCa, a weight reduction dietary modification program for PCa patients holds promise for reducing adverse patient outcomes, including PCa-specific mortality.

The precise mechanisms for obesity's influence on PCa progression have not been defined but may include alterations in the insulin-related pathways. Insulin levels increase with obesity and cancer cells require insulin for optimal growth.(9) Animal (10, 11) and human studies (12) have demonstrated a direct relationship between hyperinsulinemia and PCa growth and mortality. Several studies have found an increased relative risk in overall and advanced PCa in men with higher IGF-I levels.(13) In addition, the activity of IGF-I is modulated by the IGF binding proteins (IGFBPs), several of which are produced in the prostate.(14) The most abundant IGFBP is IGFBP-3, which has several effects on PCa cell growth including promoting apoptosis and inhibiting proliferation via both IGF-dependent and IGF-independent pathways. (15-18) While obese men do not have elevated IGF levels compared to normal- and over-weight men,(19) they have lower levels of binding proteins, which increases availability. Adiponectin is an adipokine that is inversely correlated with degree of adiposity, and which is negatively associated with risk for several cancers and with advanced prostate cancer (20-22). If the mechanism of the obesity: PCa relationship can be identified, not only could targeted therapies be administered, but also dietary interventions directed toward altering the relevant protein levels could be undertaken. The goal of our pilot study was to examine whether using a well-established dietary intervention with a track record for successful weight reduction and long-term maintenance could result in measurable changes in the insulin-related pathway activity in a randomized study of men with newly diagnosed clinically localized PCa.

Methods

The study was a randomized controlled clinical trial conducted to test the effects of a weight loss intervention within the window of opportunity between diagnostic biopsy and surgery or follow-up biopsy. Informed consent was obtained from all men and the study protocol was approved by the hospitals' human subjects review boards.

Study population

The study was comprised of men seen at either the University of Washington Urology Clinic or the Seattle-Puget Sound Veterans Affairs Hospital with newly diagnosed PCa. Inclusion criteria required (1) clinically localized disease (Gleason 3+3 or 3+4, PSA < 20, stage T1a/T2a); (2) planned treatment with either radical prostatectomy or active surveillance with planned repeat prostate biopsy; and, (3) overweight/obese (BMI ≥ 25). We excluded those with insulin dependent diabetes mellitus; those unable to undertake a caloric restriction program or who planned to join another weight loss program; and those receiving any hormonal therapy. Block randomization was performed with a computer generated program based on age and BMI (≥ 60 years of age and BMI ≥ 27.5 used as block criteria, respectively).

Intervention

The dietary intervention was a 6-weeks caloric reduction program, modified from the Diabetes Prevention Program (23, 24) lifestyle behavior change programs with goals of: 1200-2000 kcal/day and <30% daily energy intake from fat, with expected weight loss of 1-2 pounds/week. The intervention consisted of nutritional and behavioral teaching as follows: setting a calorie and fat gram goal, calorie counts of foods, how to self-monitor, and coping with challenges to eating behavior changes. Several tools were provided, such as graphs for monitoring weight, participant worksheets, cooking and shopping for lower-fat eating, and participants were encouraged to avoid replacing reduced fat calories with increased carbohydrate calories. The intervention also included several packaged modules for dealing with relapse-related issues.

The diet intervention was conducted by an experienced dietician (A.D.) who met weekly with participants. In the instances where the participant was unable to travel to meet with the dietician for a specific visit, the intervention was conducted by telephone. The intervention was individualized to the person's dietary preferences. At each meeting, the nutritionist weighed the participant, collected and reviewed calorie-count journals, and went over the participant's dietary changes from the previous week and any issues that may have arisen, providing appropriate behavioral counseling. Controls were instructed to continue their normal diet prior to surgery or repeat biopsy. The control participants then received study material on healthy diet at the end of the study and were offered an in-person meeting with the study dietician.

Assessment and data collection

Participant assessments were taken at time of randomization (baseline) and at time of surgery/repeat biopsy (end of study). Anthropometric measurements consisted of height, weight and waist (1" above umbilicus) circumference. Participants completed a 120-item food frequency questionnaire (FFQ) at baseline and end of study. Fasting serum at both time points was collected in EDTA containing tubes which were spun down, aliquoted and stored at -70°C within 2 hours of collection. Additional data on participant's medical history, physical activity levels, smoking, demographics and medications were obtained.

Assays

Fasting serum levels of insulin, c-peptide, IGF-1, adiponectin, IGFBP-1 and IGFBP-3 were determined with commercially available assays. IGFBP-1 and adiponectin were measured using ELISA kits from RayBiotech (Norcross, GA). Insulin was measured using an ELISA kit from Invitrogen (Frederick, MD). C-peptide, IGFBP-3 and IGF-1 were measured using ELISA kits from Diagnostic Systems (Webster, TX). All laboratory staff members were blinded to participant study arm and all labs were run in duplicate.

Statistical analysis

Differences in baseline characteristics between the intervention and control arms were assessed with 2-tailed t-tests. Changes in weight and reported dietary factors were determined by comparing the mean baseline and follow-up values for the two groups in a generalized estimating equation (GEE model). For the serum biomarkers, the values were not normally distributed and thus the geometric means were calculated and changes between the intervention and control groups compared with a GEE model. GEE models for dietary factors and serum biomarkers were adjusted for baseline BMI.

Results

A total of 19 men were randomized, 10 to the intervention arm and 9 to the control arm. Table 1 shows the participant characteristics by study arm. Treatment choice was radical prostatectomy in 10 men and active surveillance in 9 men (5 radical prostatectomy cases in both the intervention and control groups). Men in the control group tended to have lower weight and BMI than those in the intervention group. The median weight was 230 lbs. (range 177 – 255) and 194 lbs. (range 162 – 245) in the intervention and control groups, respectively. Similarly, the median (range) BMI was greater in the intervention group (median BMI 31.4 (range 26.3 – 38.6)) compared to the control group ((median BMI 27.6 (range 24.8 – 35.5)). In table 2, the changes between baseline and end of study weight and BMI are reported. Those in the intervention group had a 1.7% decline in body weight compared to a 0.9% decline in the control group ($p < 0.05$). The percent change in BMI was also greater in the intervention group (–1.2%) compared to controls (–0.9%, $p = 0.06$).

In Table 3, changes in dietary composition between baseline and end of study are shown. Those in the intervention group had a significantly greater decline in consumption of total calories, fat, saturated fat and starch compared to the change observed in the control group (all $p < 0.05$). An increase in dietary intake of fruits and vegetables in the intervention group was seen whereas the control group had a decline in fruit and vegetable consumption, although the change between the two groups was not statistically significant ($p = 0.27$). In Table 4, baseline and end of study serum parameters are reported. A significant difference in the change in IGFBP-3 was observed between the intervention group (2.8% change from baseline) and control group (–6.9% change from baseline, $p = 0.02$). Levels of insulin and c-peptide declined in the intervention group (–38% and –13%, respectively) whereas no change was observed in the control group (+1.6% and –1.5%, respectively). However, the difference in change between groups was not significant. Adiponectin levels increased in each group by approximately 8%. There were no differences in change in IGF-1 or in the IGF-1/IGFBP-3 ratio.

Discussion

In this randomized pilot study of a dietary intervention in men with newly diagnosed PCa, we observed a significant difference from baseline in weight loss, dietary constituent intake, and IGFBP-3 levels in the intervention group compared to the control group. Considering the growing obesity epidemic and the consistent relationship between obesity and adverse PCa outcomes, these data demonstrate the feasibility of a short-term intervention in overweight patients.

Obesity prevalence in the U.S. has risen dramatically over the past 20 years and presently more than one-third of adults are considered obese.(25) There is a strong relationship between obesity and cancer mortality with an estimated 14% of cancer deaths due to obesity. (26) This is also true in PCa, where several studies have found a 20% to 160% increased risk of PCa mortality in obese vs. normal-weight men.(1, 4, 26-29) Considering the non-cancer health benefits of maintaining a healthy weight where even small losses in body weight lead to a decreased risk of cardiovascular disease (30) and diabetes mellitus,(31) weight loss in men with PCa offers a potential opportunity to improve both overall and disease-specific survival. While other studies of caloric restriction diets in PCa have been performed, (7, 32-36) the present study diet was based on the Diabetes Prevention Program diet. This diet is individualized to take into account individual preferences and includes behavioral modification that is important for dietary adherence.(31, 37, 38)

The mechanism(s) of the relationship between obesity and adverse PCa outcomes relationship is likely multifactorial. We found significant changes from baseline between the intervention (+2.8%) and control (−6.9%) groups in IGFBP-3 ($p < 0.002$ for differences between groups). IGFBP-3 is the most abundant IGF binding protein and higher serum levels are associated with a reduction in the risk of incident and advanced PCa. (39, 40) In addition, higher IGFBP-3 levels promote apoptosis (15) and inhibit proliferation of PCa cells. (16–18) We did not find significant differences in the other proteins studied. Hyperinsulinemia has been associated with adverse PCa outcomes in men. (12, 29) In the present study, insulin levels declined by 38% only in the intervention arm, consistent with biological change with weight loss interventions, but the differences between groups was not significant.

There are several limitations to our study. First, there was some imbalance between the two groups with respect to baseline weight and BMI. We attempted to address this in our analyses by adjusting for baseline BMI. Second, cancer patients who enroll in a study of dietary intervention are more likely to be interested in and motivated to lose weight than non-participants. This was evident in the fact that weight loss was observed in those randomized to the control arm, which may have attenuated the observed differences between groups. Further, our measure of dietary intake is not optimal for measuring caloric intake. Tissue level changes in the prostate will be important for future studies. In addition, the intervention in this study was short (6 weeks) and long-term effects of weight loss maintenance will be important to demonstrate in future studies. Finally, this pilot study had limited power and thus the relatively large changes in serum biomarkers in intervention groups did not reach statistical significance when compared with controls.

In conclusion, this pilot study illustrates the ability of a short-term dietary intervention in men with PCa to lead to measurable changes in weight, dietary constituents and relevant serum proteins potentially involved in disease progression. Future larger scale studies with longer follow-up are needed to demonstrate that such changes are related to PCa outcomes. Such findings may have wide reaching application in improving both the overall and disease-specific outcomes in men diagnosed with clinically localized PCa.

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Table 1

Characteristics of participants

	Control	Intervention
Participants (no.)	9	10
Age at diagnosis		
Median (range)	60 (47 – 73)	55 (40 – 66)
40 – 49	2	3
50 – 59	2	3
60 – 69	4	4
70	1	0
Clinical T stage		
T1	6	9
T2	3	1
Gleason (baseline)		
3+3	6	8
3+4	3	2
PSA (ng/mL)		
Median (range)	4.8 (3.3 – 19)	4.4 (0.9 – 9.5)
< 4.0	2	3
4.0 – 9.9	6	7
10	1	0
Weight (kg)		
Mean (SD)	88.6 (10.2)	98.9 (12.7)
Body mass index		
Median (range)	27.6 (24.8 – 35.5)	31.4 (26.3 – 38.6)
25 – 29	7	5
30 – 34	1	4
35	1	1

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Table 3

Baseline and end of study dietary intake

	Control						Intervention					
	Baseline			End of Study			Baseline			End of Study		
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Calories (kcal)	2015	759		1787	884		2715	1809		1450	627	
			Change			%			Change			%
			-228			-11.3			-1266			-46.6
Fat (g)	85.4	38.8		81.0	53.3		108.1	83.1		47.6	24.7	
			Change			-5.1			-60.5			-55.9
Saturated fat (g)	28.8	13.6		25.7	17.5		35.1	31.1		15.5	9.9	
			-3.1			-10.6			-19.6			-55.8
Carbohydrates (g)	236	131		178	87.4		310	205		178	67.2	
			Change			-24.4			-133			-42.8
Starch (g)	79.1	33.1		67.8	32.5		117.1	88.2		56.9	21.4	
			-11.3			-14.3			-60.2			-51.4
Protein (g)	83.9	22.4		88.6	54.8		106.3	64.4		69.0	39.1	
			4.7			5.6			-37.3			-35.1
Fruit/Vegetables[^]	5.0	6.1		3.2	2.4		4.6	2.6		5.7	1.5	
			-1.8			-35.9			1.1			23.7
												0.27

* GEE model, P value comparing the difference at week 6 from baseline between Intervention and Control groups adjusted for baseline BMI.

[^] 5-A-Day Summary Method for combined daily fruit and vegetable consumption

Table 4

	Control							Intervention									
	Baseline			End of Study				Baseline			End of Study						
VAR	Geo Mean	LL	UL	Geo Mean	LL	UL	Change	%	Geo Mean	LL	UL	Geo Mean	LL	UL	Change	%	p*
C-Peptide	3.3	2.7	4.1	3.4	2.7	4.2	0.1	1.6	2.6	2.1	3.3	2.2	1.6	3.1	-0.3	-13.4	0.40
Insulin	12.8	8.3	19.6	12.6	7.4	21.4	-0.2	-1.5	11.2	7.1	17.6	6.9	4.6	10.5	-4.3	-38.1	0.30
IGF-1	137.8	89.0	213.4	166.7	115.8	239.9	28.9	20.9	179.0	114.4	280.2	209.4	133.9	327.3	30.4	17.0	0.84
IGFBP-3	76.3	66.5	87.6	71.1	59.8	84.5	-5.3	-6.9	85.8	75.8	97.1	88.2	77.8	99.9	2.4	2.8	0.002
IGF-1/IGFBP-3	1.8	1.1	3.0	2.3	1.5	3.7	0.5	29.9	2.1	1.3	3.3	2.4	1.5	3.6	0.3	13.8	0.58
Adiponectin	8.1	3.8	17.3	8.7	3.5	21.6	0.6	7.8	10.4	7.0	15.7	11.2	7.3	17.2	0.8	7.6	0.51

Geo mean: geometric mean, LL: 95% confidence interval lower limit, UL: 95% confidence interval upper limit

* GEE model, P value comparing the difference at week 6 from baseline between Intervention and Control groups adjusted for baseline BMI.