The effect of lowering cholesterol through diet on serum prostate-specific antigen levels: A secondary analysis of clinical trials

CUA PRIZE ESSAY

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Abstract

Importance: Statins appear to lower serum prostate-specific antigen (PSA) and improve prostate cancer (PCa) outcomes through cholesterol-dependent and independent mechanisms. While dietary modifications have an established role in serum cholesterol reduction, whether diet-driven cholesterol reductions yield similar PCa benefits to that observed with statins is unclear. We aimed to study the effect of diet-driven cholesterol reduction on serum PSA and estimated-PCa risk.

Methods: A total of 291 men from six published randomized controlled trials of dietary interventions were included. Men were aged ≥40 years, free of PCa, and had baseline PSA <10.0 ng/mL. Participants received one of four diets (high-fiber, low-glycemic index, low-glycemic load, or cholesterol-lowering) for 8–24 weeks. The primary outcome evaluated the association between change from baseline low-density lipoprotein cholesterol (LDL-C) and PSA. How cholesterol reduction modified PCa risk was estimated using the Prostate Cancer Prevention Trial (PCPT) risk calculator (limited to age ≥55 years, baseline PSA ≥1.0 ng/mL).

Results: Baseline PSA was 0.90 ng/mL (interquartile range [IQR] 0.55–1.60) and LDL-C was 90 mg/dL (IQR 69–125). In multivariate regression, PSA decreased 1.9% (95% confidence interval [CI] 0.55–3.2, p=0.005) per 10% reduction in LDL-C. This regression was greater in men with baseline PSA ≥2.0 ng/mL (-5.4%, 95% CI 2.2–8.6] per 10% LDL-C reduction, p-interaction=0.001). In men with estimable PCPT risk, statin-comparable LDL-C reductions (≥15%) reduced PSA by 12% (p<0.001) and estimated PCa risk by 6.5% (p=0.005).

Conclusions: This is the first study to show that serum cholesterol reduction through dietary interventions significantly lowered serum PSA and estimated PCa risk. Whether cholesterol-lowering diets improve PCa outcomes warrants investigation.

Introduction

Emerging evidence suggests a role for obesity, diabetes, and dyslipidemia in pathogenesis and prognosis of prostate cancer (PCa).[1] While a generally healthy dietary pattern may benefit PCa risk, clinical evidence supporting specific diet or lifestyle modifications that may influence prostate biology or PCa outcomes is scarce.[2] Conversely, recent studies support a role for the medications that treat cardiometabolic diseases — including the cholesterol-lowering medication, statins — and PCa outcomes. Indeed, there is an inverse association between statin-mediated cholesterol reduction and serum prostate-specific antigen (PSA),[3] and statin use appears to reduce the risk of high-grade PCa and delay the progression of advanced disease through both cholesterol-dependent and independent mechanisms.[4]

Whether serum cholesterol reduction through dietary modification yields similar benefits to statins is unknown. We thus aimed to quantify the relationship between diet-driven cholesterol reduction and serum PSA in men without PCa.

Methods

Design

This is a secondary analysis of six randomized controlled trials of four dietary interventions (low glycemic index [LGI], low glycemic load [LGL], high fiber [HF], and cholesterol-lowering [CL]) designed to evaluate between-treatment changes in cardiometabolic biomarkers over an 8–24-week study period (summarized in Supplementary Table 1; available at *cuaj.ca*).[5-10] Four trials recruited diabetic men while two recruited hypercholesterolemic men. All trials were designed by the same principal investigator. Institutional research ethics approval was obtained for each study.

Interventions were administered as dietary advice from a registered dietician with or without study-specific food provisions. Medication exposure was collected at the start of each trial through structured interviews; changes to medication use and dose were not permitted during the interventions.

Eligibility criteria

Men enrolled in the aforementioned trials with serum cholesterol and PSA data were eligible (n=309). All men were free of PCa and none reported exogenous testosterone supplementation. Men were excluded from this analysis if: age <40 years, baseline or end PSA <0.1 ng/mL or >10.0 ng/mL (Supplementary Figure 1; available at *cuaj.ca*).

Endpoints

The primary outcome evaluated the association between changes from baseline in serum PSA and low-density lipoprotein cholesterol (LDL-C). Secondary analyses evaluated other lipid biomarkers, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

Statistical analysis

Change from baseline was evaluated as opposed to between-treatment differences, as only two of six interventions were designed to elicit changes in lipid parameters as a primary outcome;[5,7] the remaining four interventions were designed to elicit changes in glycemic parameters.[6,8-10] Preliminary analyses confirmed a normal distribution for outcome data; statistical outliers were excluded if z-scores were ≤-3 or ≥3 (n=3).

Multivariable (MV) linear regressions evaluated primary and secondary outcomes. None of the a priori covariates were significant contributors to the model (age, body mass index [BMI], baseline PSA, baseline LDL-C, ethnicity, statin use, intervention, diabetes status, study year, trial duration); thus, only clinically essential covariates (age, baseline PSA, baseline LDL-C, and statin use) were included. Sensitivity analyses explored estimate modification by baseline PSA, baseline BMI, statin use, age, trial duration, and disease status. Exploratory analyses compared changes in Prostate Cancer Prevention Trial (PCPT) estimated PCa risk in men with elevated baseline risk (baseline PSA ≥1.0 ng/mL, age ≥55 years, *https://riskcalc.org/PCPTRC/*) and those who achieved statin-comparable LDL-C reductions (≥15% vs. <15%) (n=108).

Descriptive statistics and baseline characteristics are expressed as frequencies or median with interquartile ranges (IQR); differences were calculated using Chi-squared, ANOVA, or t-tests. Regressions are reported as estimates with 95% confidence interval (CI), per 10% reduction in serum cholesterol concentration. Statistical significance was established at two-sided p<0.05. Analyses were performed using R software, version 3.6.1

Results

Baseline characteristics are summarized in Table 1. Most men were Caucasian (59%), overweight or obese (78%), diabetic (86%), and statin users (62%). Median baseline PSA was 0.9 ng/mL and baseline LDL-C was 90 mg/dL.

Serum cholesterol parameters and serum PSA

Overall, serum LDL-C declined 7% (IQR -17–8.6) by the end of the study period; 30% of participants (n=88) achieved statin-comparable LDL-C reductions (≥15%). PSA decreased by 1.9% (95% CI 0.55–3.2, p=0.005) per 10% decline in LDL-C in MV models (Figure 1, Table 2). Among men achieving statin-comparable LDL-C reductions (mean observed reduction 27%), mean PSA decreased by 5.8% (p<0.001) compared to men with LDL-C reductions <15%. In secondary analyses, only serum TC was associated with PSA reductions (2.5% per 10% reduction in TC [95% CI 0.43–4.5, p=0.018]) (Table 2).

Subgroup and exploratory analyses

In subgroup regressions (Supplementary Table 2; available at *cuaj.ca*), the observed PSA reduction was greater in men with a baseline PSA ≥2.0 ng/mL (-5.4% per 10% reduction in LDL-C, 95% CI 2.2–8.6, p-interaction=0.001).

Baseline PCPT-estimated PCa risk was 17% (IQR 15–22). Among men achieving statin-comparable LDL-C reductions (≥15%, mean observed reduction 26%), PSA decreased 12% (95% CI 1.0–22, p=0.004) and PCa risk decreased 6.5% (95% CI 0.45–12, p=0.005) compared to those with <15% LDL-C reductions.

Discussion

To the best of our knowledge, this is the first study to investigate whether lowering serum cholesterol through diet impacts prostate biology. We identified a 2% reduction in serum PSA per 10% reduction in serum LDL-C achieved through dietary changes alone. In men with statin-comparable LDL-C reductions, serum PSA decreased by 6%; statin-comparable LDL-C reductions corresponded to a 7% reduction in PCPT-estimated PCa risk. Subgroup analyses suggest that men with higher baseline PSA, and thereby higher PCa risk, stand to gain the most from cholesterol-lowering diets.

These findings are in keeping with results reported for statins, wherein PSA was 4.1% lower and decreased 1.6% per 10% reduction in LDL-C.[3] Likewise, the estimated overall PCa risk reduction seen in our study is comparable to the

Table 1. Summary of baseline patient characteristics (n=291)

	Overall	Change in LDL		p
		<15% (n=203)	≥15% (n=88)	
Age, years, median (IQR)	58 (52–64)	58 (52–64)	58 (51–64)	0.63
Ethnicity, n (%)				
Caucasian	171 (59)	118 (58)	53 (60)	0.65
Asian	89 (31)	61 (30)	28 (32)	
Other	31 (11)	24 (12)	7 (7)	
BMI, kg/m^2, n (%)				
<25	63 (22)	39 (19)	24 (27)	0.31
25–29.9	129 (44)	93 (45)	36 (41)	
≥30	99 (34)	72 (35)	28 (32)	
Disease status, n (%)				
Type 2 diabetes mellitus	249 (86)	184 (91)	65 (74)	<0.001
Hypercholesterolemia[a]	42 (14)	19 (9)	23 (26)	0.38
Statin medications, n (%)				
Atorvastatin	98 (34)	70 (34)	28 (32)	0.94
Rosuvastatin	61 (21)	42 (21)	19 (22)	
Other	20 (7)	14 (7)	6 (7)	
Non-user	112 (38)	77 (38)	35 (40)	
Followup, n (%)				
≤12 weeks	186 (64)	119 (59)	67 (76)	0.004
>12 weeks	105 (36)	84 (41)	21(24)	
Dietary intervention, n (%)				
LGI	67 (23)	52 (26)	15 (17)	<0.001
LGL	51 (18)	34 (17)	17 (19)	
HF	135 (46)	102 (50)	33 (37)	
CL	38 (13)	15 (7)	23 (26)	
Serum PSA, ng/ml, median (IQR)	0.90 (0.55–1.6)	0.90 (0.60–1.6)	1.0 (0.50–1.6)	0.92
Serum LDL-C, mg/dl, median (IQR)	90 (69–125)	86 (66–108)	100 (82–151)	<0.001

[a]Hypercholesterolemia as defined as serum LDL-C ≥135 mg/dL. BMI: body mass index; CL: cholesterol-lowering; HF: high fiber; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; LGI: low glycemic index; LGL: low glycemic load.

7% risk reduction reported in meta-analyses of statin use and PCs risk.[11]

Several mechanisms may contribute to how cholesterol impacts prostate biology.[4,12] First, cholesterol is essential for systemic and prostatic androgen synthesis, and lowering circulating cholesterol levels have been shown to decrease intraprostatic androgens and slow both benign and malignant prostatic growth.[13] Second, cholesterol reduction has been shown to disrupt PCa cell lipid rafts — cell membrane microdomains that regulate intracellular survival mechanisms — inhibiting cell growth and promoting apoptosis.[14] Lastly, cholesterol reduction decreases systemic inflammation, possibly contributing to a decrease in intraprostatic inflammation and tumorigenesis.[12] Taken together, our results provide important clinical evidence supporting a statin-independent biochemical pathway between cholesterol and prostate biology.

Several limitations must be recognized. While this is a secondary analysis of randomized controlled trials, the correlational nature of this analysis restricts drawing causal inferences and raises the possibility of potential residual confounding,

Table 2. Summary of percent change in serum PSA, per 10% change in lipid parameter (n=291)

Variable	Baseline (% and IQR)*	Change from baseline (% and IQR)*	Univariate (% and 95% CI)[a]	Multivariate (% and 95% CI)[a†]
Lipid parameters				
LDL-C	90 (69 to 125)	-7.0 (-17 to 8.6)	-2.0 (-0.85 to -3.2)	-1.9 (-0.55 to -3.2)
TC	156 (133 to 193)	-4.1 (-13 to 4.6)	-2.6 (-0.76 to -4.4)	-2.5 (-0.43 to -4.5)
HDL-C	40 (35 to 46)	0.0 (-6.6 to 8.8)	-0.82 (-3.3 to 1.7)	–
TG	118 (85 to 166)	-7.4 (-26 to 17)	-0.31 (-1.2 to 0.57)	–

*Median and IQR. [a]Estimate and 95% CI per 10% change in lipid parameter. [†]Multivariate analyses were only carried out for the outcomes with significant univariate results. CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

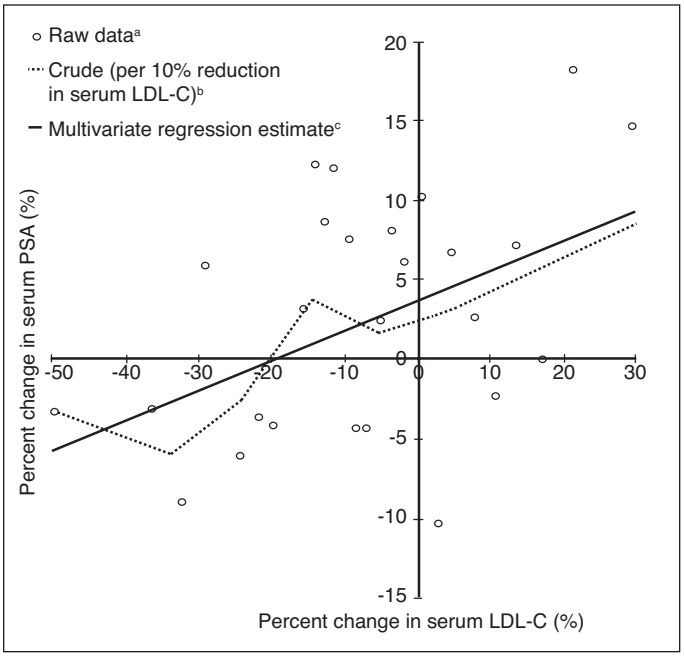

Figure 1. Multivariable linear regression of change in serum low-density lipoprotein cholesterol (LDL-C) vs. change in serum prostate-specific antigen (PSA) (n=291). [a]Each point on the scatter plot represents the averaged value of 10 raw data points, when ordered by lowest to highest percent change in serum LDL-C. [b]Crude line represents the trend by average percent change in PSA, per 10% LDL-C reduction. [c]Multivariate regression after adjusting for age, baseline LDL-C, baseline PSA, and statin use. Serum PSA decreased 1.9% per 10% reduction in serum LDL-C (p=0.005).

despite multivariate adjustments. Moreover, the possibility of altering PSA — a surrogate marker of PCa risk — without affecting cancer risk must be acknowledged; still, the pre-existing cholesterol-PSA-PCa relationship in statin-based studies[3,4] and the corresponding reduction in PCPT-estimated risk in this study support an underlying biological rationale.[15]

Conclusions

The prospect of a heart healthy, cholesterol-lowering dietary pattern simultaneously protecting against prostatic pathology is enticing. In this study, diet-driven cholesterol reductions appear to lower PSA to a similar degree to that observed with statins. Whether cholesterol-lowering diets improve PCa outcomes warrants study.

Competing interests: Dr. Fleshner has received honoraria, advisory consulting fees, and speaker bureau fees from Abbvie, Astellas, Janssen, Merck, Sanofi; has received research funding from Astellas, Bayer, and Janssen; holds stock in Verity Pharmaceuticals; has been an investigator in clinical trials supported by Astellas, Bayer, and Janssen; and is a Medical Officer for Point Biopharma. Dr. Hamilton has been an advisory board member for Astellas, Bayer, Janssen, TerSera; and has participated in clinical trials supported by Astellas, Bayer, and Janssen. Dr. Jenkins has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from Nutritional Fundamentals for Health (NFH)-Nutramedica, Saint Barnabas Medical Center, The University of Chicago, 2020 China Glycemic Index (GI) International Conference, Atlantic Pain Conference, Academy of Life Long Learning, Loblaw Companies Ltd, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative (THI), Healı Al Corp, Institute of Food Technologists (IFT), Soy Nutrition Institute (SNI), Herbalife Nutrition Institute (HNI), Herbalife International, Pacific Health Laboratories, Nutritional Fundamentals for Health (NFH), the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), and the American Society of Nutrition (ASN). He is a member of the International Carbohydrate Quality Consortium (ICQC). He has also received in-kind supplies for trials as a research support from the Almond board of California, Walnut Council of California, the Peanut Institute, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, and WhiteWave Foods, and has received research grants from Loblaw Companies Ltd., the Almond Board of California, Soy Nutrition Institute (SNI), and the Canadian Institutes of Health Research (CIHR). The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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