Phase II prospective randomized trial of weight loss prior to radical prostatectomy

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Abstract
Background Obesity is associated with poorly differentiated and advanced prostate cancer and increased mortality. In preclinical models, caloric restriction delays prostate cancer progression and prolongs survival. We sought to determine if weight loss (WL) in men with prostate cancer prior to radical prostatectomy affects tumor apoptosis and proliferation, and if WL effects other metabolic biomarkers.

Methods In this Phase II prospective trial, overweight and obese men scheduled for radical prostatectomy were randomized to a 5–8 week WL program consisting of standard structured energy-restricted meal plans (1200–1500 Kcal/day) and physical activity or to a control group. The primary endpoint was apoptotic index in the radical prostatectomy malignant epithelium. Secondary endpoints were proliferation (Ki67) in the radical prostatectomy tissue, body weight, body mass index (BMI), waist to hip ratio, body composition, and serum PSA, insulin, triglyceride, cholesterol, testosterone, estradiol, leptin, adiponectin, interleukin 6, interleukin 8, insulin-like growth factor 1, and IGF binding protein 1.

Results In total 23 patients were randomized to the WL intervention and 21 patients to the control group. Subjects in the intervention group had significantly more weight loss (WL: −3.7 ± 0.5 kg; Control: −1.6 ± 0.5 kg; p = 0.007) than the control group and total fat mass was significantly reduced (WL: −2.1 ± 0.4; Control: 0.1 ± 0.3; p = 0.015). There was no significant difference in apoptotic or proliferation index between the groups. Among the other biomarkers, triglyceride, and insulin levels were significantly decreased in the WL compared with the control group.

Conclusions In summary, this short-term WL program prior to radical prostatectomy resulted in significantly more WL in the intervention vs. the control group and was accompanied by significant reductions in body fat mass, circulating triglycerides, and insulin. However, no significant changes were observed in malignant epithelium apoptosis or proliferation. Future studies should consider a longer term or more intensive weight loss intervention.

Introduction

Obesity is associated with poorly differentiated and advanced prostate cancer, increased risk of biochemical failure following radical prostatectomy and radiation therapy, and increased prostate cancer mortality [1–8]. Multifactorial mechanisms may explain the link between obesity and the increased risk of advanced prostate cancer. Insulin...
metabolism, IGF-1, IGF binding protein, altered serum levels of sex hormones, pro-inflammatory cytokines, and adipokines may be involved [9–12]. Visceral obesity may play an important role in the link between obesity and development of prostate cancer. One study among men in China showed that men in the highest quartile of waist-to-hip ratio had an almost three-fold increased risk of developing prostate cancer [13]. Another study described that central body fat mass was associated with increased high-grade prostate cancer [14]. Likewise, increased periprostatic fat mass was associated with higher Gleason grade [15–17].

Whether weight loss (WL) has the potential to delay prostate cancer progression is of great interest. In preclinical studies, energy restriction is well-known to decrease prostate cancer progression and prolong survival in mouse models [18–21]. The IGF-AKT pathway, cytokines and adipokines, and microvessel density/vascular endothelial growth factor (VEGF) gene expression play a role in the decrease of prostate cancer progression in mouse models [18, 19, 21]. However, evidence from human studies is inconclusive [22]. To examine if WL has the potential to slow the progression of prostate cancer, we designed a prospective randomized pre-prostatectomy trial to determine whether WL from a hypocaloric diet and increased physical activity results in anti-proliferative and pro-apoptotic effects on prostate cancer tissue histopathology. Other examined endpoints included weight change, body composition and fat depots, and concentrations of potential mechanistic markers such as serum lipids, cholesterol, insulin, IGF-1, IGFBP-3, leptin, adiponectin, IL-6, IL-8, testosterone, and estradiol.

Materials and methods

Patient eligibility and recruitment

Participants were recruited from the urology clinics at the Veterans Administration Greater Los Angeles Healthcare System, UCLA, and Santa Monica UCLA from 2009 to 2013. Inclusion criteria included BMI of >25 kg/m², physical ability to undergo a physical activity intervention, and able to come to the VA Clinical Research Center for seven study visits if randomized to the WL group. Subjects were ineligible if they had Gleason score $>$4 + 5 = 9, a history of receiving androgen deprivation therapy, antiandrogen therapy, finasteride, radiotherapy, or cryotherapy. Patients were also excluded if they had a history of diabetes and were receiving insulin, if they were taking weight loss medication or enrolled in a weight loss program, taking lycopene supplements, or had significant co-morbidities (i.e., cardiac, pulmonary, liver disease, and ongoing alcohol/drug abuse) or a cardiac pacemaker. The study was approved by the Institutional Review Boards at the VA and UCLA and registered with ClinicalTrials.gov (NCT#00475982).

Study design

This was a randomized two-arm open label intervention study. All subjects signed informed consent documents prior to study entry. Subjects were randomized using a permuted block design to either a weight loss program or control group. After randomization, baseline weight, height, waist, hip circumference, and body composition by dual-energy X-ray absorptiometry (DEXA) (GE Lunar DEXA, Chicago, IL; maximum weight capacity 350 lbs) were determined, and fasting blood was collected. The control group proceeded with the scheduled radical prostatectomy. Within 3 days prior to radical prostatectomy, the control group had one additional visit to the clinical research center (CRC) for measurement of weight, height, waist, hip circumference, and fasting blood collection. Performance of a second DEXA scan in the control group prior to radical prostatectomy was added as a protocol modification after the beginning the trial, and therefore the first nine participants in the control group did not have an end of study DEXA scan. The control group was offered a free weight loss program after prostatectomy.

Subjects randomized to the WL group received one of two standard structured energy-restricted meal plans (1200 and 1500 Kcal/day) using commercially available meal replacements and portion-controlled foods. Patients were taught how to count portions and how to consume the recommended calories from commercial ready-made frozen dinners. Prescribed plans were based upon lean body mass as determined by DEXA. The goal of the meal plan was to provide a total calorie intake incorporating 500–800 calorie deficits per day. Subjects had weekly visits with the CRC diettian for the first 4 weeks, and every 2-week visits for the following 4 weeks and received instruction on recipes, grocery shopping strategies, education on healthy food preparation, and preparation of meal replacements. Prior to each visit, subjects in the WL group completed a 3-day food record to promote compliance and as a tool to assist the diettian with counseling. Subject’s wives or life partners were encouraged to attend and participate in the sessions. The goal for recommended diets was to contain 20–25% energy from fat, 15–20% from protein, and 50–65% from carbohydrates largely from fruits and vegetables with some whole grains. Fiber recommendations were a total of 25 g/day from fruits, vegetables, legumes, and high fiber cereals.

Patients in the WL group were counseled on performing 1 h of exercise/day including aerobic, resistance, and flexibility activities such as walking and stretching. As an exercise incentive, patients were provided pedometers (Omron HJ-112 Digital Premium Pedometer, Bannockburn,
IL) and exercise logs to complete and results were reviewed with the dietitian at each visit. As shown by Bravata et al., the use of pedometers is associated with significant increase in physical activity [23]. Following the 5–8-week weight loss intervention and within 3 days prior to radical prostatectomy, weight, height, and waist to hip ratio were measured, fasting serum for biomarker analysis collected, and a DEXA scan was performed.

Outcomes

The primary endpoint was apoptotic index in the radical prostatectomy malignant epithelium. Secondary endpoints were proliferation (Ki67) in the radical prostatectomy malignant epithelium, body weight, BMI, waist to hip ratio, body composition, and serum PSA, insulin, triglyceride, cholesterol, testosterone, estradiol, leptin, adiponectin, IL-6, IL-8, IGF-1, and IGFBP-1 levels.

Serum analyses

Serum PSA, triglyceride, total cholesterol, LDL- and HDL-cholesterol, insulin, testosterone, and estradiol were measured by the UCLA clinical laboratory using standard laboratory methods. Serum leptin and adiponectin concentrations were measured using ELISA kits according to manufacturer instructions (Invitrogen, Carlsbad, CA) with coefficient of variation (CV) for leptin: Intra-assay CV 3.0–3.8% and inter-assay CV 3.9–4.6% (147–884 pg/mL), and adiponectin intra-assay CV 3.8–3.0% and inter-assay CV 5.2–2.8% (1.9–24.8 pg/mL). Serum IL-6 and IL-8 were quantified using ELISA kits from BD Biosciences (San Jose, CA) according to instructions with the following CV for IL-6: Intra-assay CV 4.1–10.8% (43.6–146.9 pg/mL) and inter-assay CV 10.9–7.9% (39.1–147.8 pg/mL) and IL-8: Intra-assay CV 4.2–5.5% (27.4–92.1 pg/mL) and 3.4–3.2% (27.2–99.9 pg/mL).

Plasma IGF-1 and IGFBP-1 concentrations were determined using a validated ‘in-house’ ELISA assay at the University of Southern California Aging Biomarker Service Core (Los Angeles, CA) with CV <10% [24].

Immunohistochemistry

Serial sections for immunohistochemical analyses were cut from archived paraffin embedded blocks with the largest cancer volume and with the Gleason grade corresponding to the grade on the final pathology report. Slides were stained for Ki67 (monoclonal mouse anti-human Ki67 antigen (Dako Omnis/Agilent, Santa Clara, CA)) and TUNEL (ApopTag® Plus Peroxidase In Situ Apoptosis Kit (Millipore, Temecula, CA)) [25] to assess proliferation and apoptosis, respectively. The areas of adenocarcinoma were circled by the study pathologist (JS) Slides were digitized on a ScanScope AT (Aperio Technologies, Inc., Vista, CA) and morphometric analysis performed with Definiens’ Tissue Studio (Definiens Inc., Parsippany, NJ) to determine the percentage of Ki67 or TUNEL positive cells in a non-biased method. Briefly, using the pre-defined nuclear detection module and classification tool, positive and negative nuclei within each region of interest were identified. Thresholds were set to classify hematoxylin stain for negative nuclei and DAB stain for positive nuclei. The data were exported to Excel for further statistical analysis. The number of Ki67 or TUNEL-stained nuclei per total cells in the adenocarcinoma region was used to calculate the percent of positive stained cells [26]. Scanning and analyses were performed through the Translational Pathology Core Laboratory, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA.

Statistical analysis

A sample size of 65 subjects (no weight loss = 35, weight loss = 30) was estimated to provide 80% power to detect an effect size of 0.74 using a two group t-test with a 0.050 twosided significance when comparing the apoptotic index (primary outcome variable) in the radical prostatectomy malignant epithelium between the WL and no WL groups. To put this effect size in context, a similar study looking at a nutritional intervention by Kim et al. observed an effect size of 1.81 on apoptotic index using a nutritional intervention with similar study characteristics [27]. To account for a post-randomization attrition rate of up to 15% in the WL group, we planned to randomize 35 subjects to the WL group.

After 34 subjects fully completed the trial, an interim analysis was performed to evaluate the feasibility of finding a statistically significant difference between the groups for the primary outcome. A conditional power analysis demonstrated that, with enrollment of 65 participants, there was only a 0.9% chance of finding a significant difference in the apoptotic index between the treatment and control group. At this point, study enrollment was closed and secondary endpoint analyses were performed.

Baseline patient characteristics were compared between groups using mean ± SD and frequencies. Secondary outcomes were measured both at baseline and prior to surgery and change from baseline to surgery was calculated. Within each group, changes from pre to post were calculated using the paired t-test. Next these changes were compared between control and WL intervention groups using the two sample t-test. For outcomes that had skewed distribution, a log transformation was imploded prior to conducting the t-test. P values <0.05 were considered significant. Statistical analyses were carried out using IBM SPSS V24.
The mean time from study enrollment until radical prostatectomy was 62 ± 19 days in the control group and 51 ± 16 days in the WL group. Although patients had significant WL in both groups, subjects on the WL intervention had more weight loss (−3.7 ± 1.9 kg) compared with the control group (−1.9 ± 2.3 kg) (Table 2, Fig. 2). Patients in the WL group also had a greater decline in BMI (−1.2 ± 0.6) as compared with the control group (−0.5 ± 0.7) (Table 2). The WL intervention group had a greater decrease in fat mass (WL group −2.1 ± 1.8 vs. control group 2.2 ± 6.2) and decrease in percent gynoid fat (WL group 1.4 ± 1.9 vs. control group 0.2 ± 1.3, Table 2). There was a trend for a greater decrease in percent body fat in the WL group (p = 0.06) vs. the control group. No significant change was observed in lean body mass, percent trunk fat, and percent android fat between the groups.

Prostate cancer tissue apoptosis and proliferation

There was no significant difference in apoptotic index in radical prostatectomy tumor tissue (Primary Endpoint) as measured by TUNEL between the groups (Fig. 3a). Likewise, there was no significant difference in the proliferation index, as measured by Ki67 staining between the groups (Fig. 3b).

Serum lipid, adipokine, hormone, cytokine, and IGF/IGFBP-1

During the intervention period, there was a significant 33% decrease in serum triglyceride from 208 ± 194 to 140 ± 79 mg/dL in the WL group, while triglycerides increased in the control group from 131 ± 51 to 138 ± 71. Likewise, serum insulin levels decreased in the WL group from 17 ± 10 to 13.8 ± 7 and increased in the control group from 12 ± 7 to 14 ± 9 µIU/mL. There was no significant difference in serum total cholesterol or HDL-cholesterol between the WL and control groups (Table 3). There was a significant between group difference in LDL-cholesterol levels with a decrease in the control group as compared to the WL group. There were no significant between group changes in adipokines, testosterone, estradiol, IL-6, IL-8, IGF-1, and IGFBP-1 levels.

Table 1 Baseline characteristics of study participants

|                     | Control (n = 18) | Weight Loss (n = 16) |
|---------------------|-----------------|----------------------|
| **Ethnicity**       |                 |                      |
| Caucasian (No.)     | 14              | 11                   |
| Black American (No.)| 3               | 5                    |
| Hispanic (No.)      | 1               | 0                    |
| **Age (y), mean ± SD** | 61.7 ± 1.5     | 63.4 ± 1.2           |
| **PSA (ng/mL; mean ± SD)** | 7.5 ± 1.9       | 6.8 ± 0.6            |
| **BMI pre**         | 31.7 ± 1.1      | 32.9 ± 1.5           |
| **Gleason sum at diagnosis (No.)** | 6              | 7                    |
| 6                   | 6               | 4                    |
| 7                   | 8               | 9                    |
| 8–9                 | 4               | 3                    |
| **No. of positive cores** | 33–96           | 29–89                |

Values presented as Mean ± SEM or frequency

(Armonk, NY). The data are presented as mean ± SD or SEM where appropriate.

**Results**

**Baseline characteristics**

In total 23 patients were randomized to the WL intervention and 21 patients to the control group. Seven patients in the WL group and three from the control group withdrew from the study with 34 patients completing the trial (Fig. 1). The baseline characteristics of the 34 patients that completed the trial are shown in Table 1. All participants were overweight or obese. In the WL group, 44% were overweight, 44% obese, and 12% morbidly obese at baseline, while, in the control group, 31% were overweight, 44% obese, and 25% morbidly obese. A total of 67% of patients in the control group and 69% in the WL group were taking statins. The mean PSA in the WL group was 6.8 ± 2.5 compared with control group 7.5 ± 8.0 (Table 1). There was no significant difference in age, race, ethnicity, statin use, Gleason Score, and disease stage between the two groups (Table 1).

**Body weight and composition**

The mean time from study enrollment until radical prostatectomy was 62 ± 19 days in the control group and 51 ± 16 days in the WL group. Although patients had significant WL in both groups, subjects on the WL intervention had more weight loss (−3.7 ± 1.9 kg) compared with the control group (−1.6 ± 2.3 kg) (Table 2, Fig. 2). Patients in the WL group also had a greater decline in BMI (−1.2 ± 0.6) as compared with the control group (−0.5 ± 0.7) (Table 2). The WL intervention group had a greater decrease in fat mass (WL group −2.1 ± 1.8 vs. control group 2.2 ± 6.2) and decrease in percent gynoid fat (WL group 1.4 ± 1.9 vs. control group 0.2 ± 1.3, Table 2). There was a trend for a greater decrease in percent body fat in the WL group (p = 0.06) vs. the control group. No significant change was observed in lean body mass, percent trunk fat, and percent android fat between the groups.

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Discussion

Obesity is a well-established factor associated with increased risk and mortality of a number of human malignancies [28]. Given the well-known impact of obesity on prostate cancer aggressiveness and mortality and the significant effect of caloric restriction on prostate cancer progression in preclinical models, there is strong evidence to support the conduct of clinical trials evaluating WL as a therapy for men with prostate cancer. Although the short-term WL intervention in our trial did not impact apoptosis or proliferation in radical prostatectomy malignant epithelium, biomarker results from our trial and others suggest the potential for clinical benefit of WL for men with prostate cancer. For example, a significant reduction in percent body fat was observed over the course of the trial. Previous studies showed that central body fat mass was associated with increased high-grade prostate cancer [14]. Likewise, increased periprostatic fat mass was also associated with higher Gleason grade [15–17]. Iyengar et al. recently reviewed the pro-inflammatory and pro-carcinogenic effects of hyperadiposity on the tumor microenvironment, and discussed the link between chronic low-grade inflammation and hyperinsulinemia [29]. Noteworthy, in the current study circulating insulin levels were also reduced in the WL group (−18% compared with +18% in the control group), and insulin is a known growth factor for prostate cancer.

A number of short-term clinical studies examined whether WL favorably modifies hormonal factors associated with prostate cancer progression. A small \((n=11)\) short-term intensive WL intervention with a very low fat diet (<10% kcal from fat) in overweight and obese men was found to modify serum factors (IGF-1 decreased by 20%, IGFBP-1 increased by 53%, and insulin decreased by 25%) and decreased serum-stimulated growth of LNCaP cells was observed in an ex-vivo bioassay [30]. It is noteworthy that patients lost more weight in this trial (4.2% WL over an 11-day period) as compared to our trial (1.5%WL in the control group and 3.7% WL in the treatment group), and in our trial IGF-1 and IGFBP-1 levels did not change. Given that the IGF axis may play a key role in the effects of weight loss on prostate cancer, it may be that the degree of weight loss in our trial was not adequate to affect tissue apoptosis. In another trial, Lin et al. reported that a 6-week low-fat, low-glycemic load diet resulted in significant WL (5.5%) and gene expression changes in 26 genes comparing biopsy tissue collected before and after diet intervention [31]. In another small randomized trial, a 6-week caloric restricted diet in men with prostate cancer resulted in significant WL (−1.7%) and an increase in serum IGFBP-3 (+2.8%) compared to controls (WL+1%, IGFBP-3–6.9%) [32]. No significant changes in serum insulin, IGF-1 and adiponectin were observed [31]. Heymach et al. conducted a controlled prospective randomized 4-arm pre-prostatectomy trial incorporating a low-fat diet and flax seed. They reported that WL significantly

- **Table 2**: Changes in body composition

| Study outcomes | Control Post-intervention minus pre-intervention | WL Post-intervention minus pre-intervention | \(P\)-value |
|---------------|-----------------------------------------------|---------------------------------------------|------------|
| Weight (kg)   | \(-1.6 \pm 0.5\)                              | \(-3.7 \pm 0.5^{**}\)                       | \(0.007\) |
| BMI (kg/m²)   | \(-0.5 \pm 0.2\)                              | \(-1.2 \pm 0.6^{**}\)                       | \(0.005\) |
| Waist (cm)    | \(-0.4 \pm 0.2\)                              | \(1.0 \pm 0.3\)                             | 0.113      |
| Hip (cm)      | \(-1.2 \pm 0.7\)                              | \(-0.5 \pm 0.45\)                           | 0.390      |
| Fat mass (kg) | \(0.1 \pm 0.3\)                               | \(-2.1 \pm 0.4^{*}\)                       | \(0.015\) |
| Lean mass (kg)| \(-0.7 \pm 0.4\)                              | \(-1.6 \pm 0.6\)                           | 0.304      |
| Body fat (%)  | \(0.4 \pm 0.3\)                               | \(-0.9 \pm 0.5\)                           | 0.063      |
| Trunk fat (%) | \(0.6 \pm 0.4\)                               | \(-0.9 \pm 0.7\)                           | 0.125      |
| Gynoid fat (%)| \(0.2 \pm 0.4\)                               | \(-1.4 \pm 0.5^{*}\)                       | \(0.032\) |
| Android fat (%)| \(0.6 \pm 0.3\)                             | \(-1.0 \pm 0.8\)                           | 0.156      |

Data represent mean ± SEM. \(N=18\) for control and \(n=16\) for WL group. Within each group the difference between baseline and end of intervention was evaluated using paired \(t\)-test; \(^{*}p≤0.05\), \(^{**}p<0.01\). Changes between groups were calculated using two independent sample \(t\)-test; bold values indicate statistically significant \(p\)-values.

![Waterfall plot of weight loss](#)
correlated with reduction in plasma VEGF levels, TNF-related apoptosis-inducing ligand (TRAIL) levels, and five other pro-inflammatory cytokines [33]. Fabian et al. demonstrated a 10% weight loss along with a significant decrease in Ki67 staining in breast cancer tissue [34]. Another pre-prostatectomy weight loss study is ongoing [35]. These investigators reported 9% weight loss in the intervention group and 6.2% weight loss in the control group, but have not yet reported on changes in tumor biomarkers [36].

A number of mechanisms have been proposed linking obesity to advanced prostate cancer. As shown in animal studies, alterations in insulin metabolism, IGF-1, IGF binding protein, altered serum levels of sex hormones and pro-inflammatory cytokines, and adipokines might be involved [37, 38]. The IGF axis is a frequently investigated target in prostate cancer since it plays an important role in cell proliferation, cell differentiation, apoptosis, and glucose and lipid metabolism [39]. In a previous study by our group, long-term consumption of a low-fat/high-fiber diet, including soy for 6 months in prostate cancer patients following radical prostatectomy resulted in decreased serum IGF-1 compared with the consumption of the USDA recommended diet [40]. In the present trial, we did not find any change in IGF-1 or IGFBP-1.

In the current trial, we found a decrease in serum triglycerides, total cholesterol, and fat mass, which was expected with WL. A recent meta-analysis found that there was no relationship between serum triglyceride and prostate cancer risk [41]. Although a decrease in fat mass may potentially result in a decrease of inflammatory cells in adipose tissue, we did not find any decrease in serum IL-6 or IL-8 levels.

Noteworthy, in our present trial, there was significant WL in the control group (−1.6 ± 2.3 kg). However, between group comparisons demonstrated significantly more WL in the intervention group (−3.7 ± 1.9 kg) as compared to the control group. Through the standard consenting process, research subjects are aware of general aspects of the control and intervention groups and often desire randomization to the intervention group. Our trial and others demonstrated that patients randomized in the control group often self-implement behavioral changes and, in this case, achieved WL [42]. In our trial, the incremental difference in weight loss between the intervention and control group was relatively low at 2.1 kg. Weight loss in the control group also occurred in other studies [36]. Consideration should be given to implementing active interventions in the control group to prevent WL. Future trials should also consider more intensive weight loss interventions to achieve a greater difference in weight loss between the treatment and control groups. In this regard, data from our trial may be useful for power calculations for future randomized WL intervention trials in men with prostate cancer.

A number of study designs may be appropriate for future WL intervention trials in men with prostate cancer.
example, men on active surveillance undergoing targeted same
sight biopsies may be an ideal study population to undergo a
long-term intervention. Another population to consider would
be men on androgen deprivation for prostate cancer. Androgen
deprivation is known to increase body fat, making this
potentially an ideal population for future studies [43]. In a
prospective randomized trial incorporating diet and exercise,
O’Neill et al. reported significant WL, reduction in total body
fat, and improved functional capacity in men on androgen
deprivation therapy, though they did not report on biomarkers
related to prostate cancer progression [44].

There are several limitations to our study. Our trial was a
short-term pre-prostatectomy trial, and a longer intervention
may be required to observe tissue biomarker changes as a
result of WL. Men in the study lost on average 0.5 kg per
week. It appears that participants did not completely follow
the dietary instructions as they should have lost more
weight if eating a 1200 or 1500 kcal diet. The compliance
measure in the present study was weight loss. We did not
report food intake data and pedometer readings. This
information may potentially be useful for designing future
trials and evaluating compliance. A number of pre-
prostatectomy dietary intervention trials incorporating
dietary supplements such as fish oil and flax seed, and
increased dietary intake of lycopene rich tomato sauce
reported changes in tissue biomarkers, but WL without a
specific focus on selected dietary nutrients may require
longer term interventions [27, 45]. In addition, our trial was
offered to all overweight and obese patients undergoing
radical prostatectomy at the VA and UCLA. Future research
should focus on selecting out specific patients more likely to
respond to WL interventions based on inflammatory
markers and thus incorporate “precision medicine” markers
prior to enrollment.

Conclusion

In summary, our short-term WL program prior to radical
prostatectomy resulted in significantly more WL in the inter-
vention vs. the control group and was accompanied by sig-
ificant reduction in body fat mass, circulating triglycerides,
and insulin levels. However, there were no significant changes
in malignant epithelium apoptosis or proliferation levels. On
the basis of the known association of obesity and lethal
prostate cancer, future longer-term or more intensive weight
loss intervention trials are warranted to further examine if WL
has therapeutic benefits in men with prostate cancer.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing
interest.

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