

The Comparison and Estimation of the Prognostic Value of Lipid Profiles in Patients With Prostate Cancer Depends on Cancer Stage Advancement

American Journal of Men's Health
2017, Vol. 11(6) 1745–1751
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DOI: 10.1177/1557988317717382
journals.sagepub.com/home/ajmh


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Abstract

Lipid profiles and prostate cancer have a controversial relationship, and the predictive ability of lipids in determining cancer risk estimation is still questionable. This study demonstrates a significance assessment of the plasma lipid profiles of subjects with prostate cancer. Locoregional subjects irradiated with external beam therapy were compared to prostate cancer subjects with bone metastases. The histopathologic diagnosis of 103 subjects (71 locoregional [Group 1] and 32 palliative [Group 2]) were analyzed and compared using their blood samples, total cholesterol (CHL), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. The HDL/CHL, LDL/CHL, and TG/HDL ratios were used for better fit and comparison. Subjects were grouped according to their cancer stages and assessed using statins in both groups. In this study, serum HDL/CHL was significantly increased in Group 1 compared to Group 2 ($p = .02$), and time–statin factor in relation was statistically significant ($p = .02$). For Group 2, this index decreased with each day after radiotherapy ($p = .07$), which means the CHL was increased. Negative effects were noticed at the time of observation of the LDL/HDL ratio with an approximate increase of 0.0025 each day in palliative subjects. This ratio showed a statically significant elevation ($p = .04$). There was not a statistically significant difference in the value of the TG/HDL ratio between both groups. As the survival of cancer subjects increases, frequent control of the lipid profile gains importance.

Keywords

cholesterol, high-density lipoprotein, low-density lipoprotein, prostate cancer, radiotherapy, triglycerides

Received December 29, 2016; revised May 16, 2017; accepted May 17, 2017

Cholesterol is required for the normal growth of cells and their maintenance. It is one of the elements that is important in the accumulation of testosterone (Simons & Ikonen, 2000). Since 1909, White (1909) and other authors, including: Jowett, Yasuda and Bloor, noticed that cholesterol accumulated in malignant tissues (Jowett 1931; Yasuda & Bloor, 1932), which is now regarded as a feature of cancer cells (Freeman & Solomon, 2004). Prostate cancer cells proliferate in response to androgens via the nuclear androgen receptor. Androgen is produced by steroidogenesis, and cholesterol is the precursor in this process (Murai, 2015). The pattern of lipid serum levels in localized and metastatic prostate cancer is unknown, but

cholesterol may play a critical role in the progression of prostate cancer.

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Materials and Methods

Subjects' Characteristics

This is a cross-sectional study of 103 Caucasian men who were treated with external beam radiotherapy for locoregional or for metastatic prostate cancer in the radiotherapy department of the Regional Clinical Hospital of Zielona Gora. This study was approved by the ethics committee and consent from the subjects was received. The study was conducted by one physician over a period of 3 years between 2012 and 2015. Among the patients, 71 men received prostate radiotherapy only without nodal pelvis treatment, and 32 men received palliative radiotherapy to treat bone metastases only without palliative prostate radiotherapy. Blood samples were collected before starting radiotherapy (on a fasting morning and before the initiation of androgen deprivation therapy [ADT] administration) and evaluated by measuring the lipid serum levels. The lipid profiles were monitored in subjects every 2 to 3 months after the completion of radiation therapy and then every 3 to 6 months thereafter. Lipid serum levels were assessed using CD 3700 and CD Ruby, Abbott, kilt chemistry analyser and ACL Top, Werfen company, USA.

In hospital, the reference values for the normal ranges of the measured levels are as follows: Total cholesterol (CHL) is 130 to 200 mg/dL, high-density lipoprotein (HDL) cholesterol is 35 to 80 mg/dL, low-density lipoprotein (LDL) cholesterol is 50 to 130 mg/dL, and triglycerides (TG) are 65 to 150 mg/dL. The subjects were categorized according to TNM clinical stage (T—primary tumor site, N—regional lymph node, and M—metastatic spread). For the purpose of this analysis, the subjects were divided into two groups: Group 1—locoregional disease (T₁₋₃NoMo) and treated with radical radiotherapy, and Group 2—subjects with metastases treated with palliative radiotherapy to bones only. ADT was utilized in the treatment of the locoregional group (Group 1; 50 patients—70% of the group) and metastatic prostate cancer (32 patients—100% of Group 2). Only subjects with a Gleason score of ≤6 and with prostate-specific antigen (PSA) <10 ng/mL did not receive hormonal therapy (21 patients). The subjects' characteristics are summarized in Table 1. A medical history was obtained including medical comorbidities. Subjects were asked about the use and duration of treatment with statins, and their lipid profile levels were determined. Two subjects from Group 2 were taking antidiabetic drugs and they used metformin hydrochloride.

The norms of known atherogenic parameters were used to calculate the cholesterol ratios, which were as follows: HDL/CHL > 0.24, LDL/HDL < 3.5, and TGL/HDL ≤ 2. These components were indicators of lower cardiovascular risk and are of greater predictive value than the

Table 1. Patient and Clinical Tumor Characteristics in 103 Patients.

Characteristics	No. of patients: 103 (100%)
Age:	
Median (range)	71 (54–87)
80–87	20 (19)
70–79	40 (39)
60–69	37 (36)
50–59	6 (6)
ECOG performance status:	
0	13 (13)
1	43 (42)
2	47 (48)
Histologic diagnosis:	
Adenocarcinoma	103 (100)
Differentiation:	
Gleason score 2–6	42 (41)
Gleason score 7	27 (26)
Gleason score 8–10	37 (36)
Serum PSA*, ng/mL	
< 10	30 (29)
11–20	24 (23)
>20	49 (51)
Statin use:	22 (21)
ADT*, use:	
Group 1	50 (70)
Group 2	32 (100)
Antidiabetic drugs:	
Metformin hydrochloride	2 (2)

Note. ECOG = Eastern Cooperative Oncology Group; *PSA = prostate-specific antigen; *ADT = androgen deprivation therapy.

isolated parameters. All subjects survived up to or close to the conclusion of the study.

Radiotherapy

Seventy-one locally advanced subjects received metallic markers in the prostate gland. The radiation procedure was performed using a 6 MV and 15 MV photon beam for both intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) with a conventional fractionalization of 2 Gy per fraction with a total dose of 76 Gy. The procedure was continued for 5 consecutive days per week. Thirty-two palliative subjects received 2D conformal radiotherapy (CRT) with a conventional fractionalization of 4 to 8 Gy with a total dose of 6 to 20 Gy.

Statistical Analysis

Multilevel modeling was performed during the statistical analysis (see, e.g., Raudenbush & Bryk, 2002). In this

Table 2. Multilevel Modeling of Group 1, Locoregional With Radical Radiotherapy, and Group 2, Metastases Treatment With Palliative Radiotherapy.

Ratio	Group of radiotherapy	Regression coefficient	Mean	Standard error	p value
HDL/CHL	1	Intercept	0.258	0.04	<.0001
		Days	0.0002	0.0001	.0226
		Statin	0.0165	0.0218	.4509
		Days*statin interaction	-0.0001	0.00004	.02
	2	Intercept	0.4026	0.2142	.067
		Days	-0.0003	0.0002	.0752
		Statin	-0.0648	0.1081	.5522
		Days*statin interaction	0.0002	0.0001	.0689
LDL/HDL	1	Intercept	2.0845	0.412	<.0001
		Days	-0.001	0.0007	.183
		Statin	0.0877	0.2296	.7035
		Days*statin interaction	0.0005	0.0004	.2031
	2	Intercept	-0.7644	2.7803	.7846
		Days	0.005	0.0024	.0421
		Statin	1.6104	1.4031	.2571
		Days*statin interaction	-0.0025	0.0012	.0474
TGL/HDL	1	Intercept	3.7825	1.5035	.0138
		Days	0.0011	0.0027	.6748
		Statin	-0.106	0.8458	.9006
		Days*statin interaction	-0.0004	0.0016	.8238
	2	Intercept	1.1583	4.8814	.8136
		Days	0.0045	0.0046	.3314
		Statin	0.8008	2.457	.7461
		Days*statin interaction	-0.0024	0.0023	.3138

Note. HDL = high-density lipoprotein; CHL = total cholesterol; LDL = low-density lipoprotein; TGL = triglyceride.

approach, statistical models are viewed as generalizations of linear models and rely on a nested random analysis of variance. The computations were conducted using the R platform (R version 3.2.2, 2015), (<http://www.r-project.org>). The interaction between time and statin administration effects with the concentration ratios were studied using linear regression with random effects (ratio = intercept + days*statin).

Results

In Group 1, there were 71 patients, and out of this group, 50 patients took ADT and 21 didn't. In comparison, no statistical influence on the analyzed concentration ratios regarding these 2 subgroups in Group 1 was identified.

As reported in Table 2, a positive effect of HDL/CHL ratio with an approximate increase of 0.0002 ($p = .02$) per day after the radiotherapy in Group 1 can be seen. Moreover, there was no impact of unaccompanied statin administration noticed in patients and this effect was random itself ($p = .45$). However, the relation between time and the statin application was statistically significant and there was an HDL/CHL ratio reduction of approximately

0.0001 per day during the study period ($p = .02$). It is of note that for Group 2, the HDL/CHL ratio trends (on the border of statistical significance) are opposite to the results above, that is, time effect is negative and it is equal to 0.0003 per day of observation ($p = .07$), whereas time and statin interaction = 0.0002 ($p = .06$), respectively (see results in Table 2). The study identified that serum HDL/CHL was significantly increased in Group 1 compared to Group 2, ($p = .02$). It was also identified that the time of statin factor interaction was statistically significant ($p = .02$). For Group 2 subjects, this index decreased each day after radiotherapy ($p = .07$), indicating that the CHL increased. Regarding the LDL/HDL ratio, no statistical influence on its level of time and drug administration (unaccompanied and interacted) was observed in subjects in Group 1. However, in Group 2, a statistically significant increase of the LDL/HDL ratio was noted of approximately 0.005 per day during the study period ($p = .04$), together with a concurrent effect of time and statin administration, which was decreasing 0.0025 per day within the same timeframe ($p = .04$). In turn, based on the estimated p values (see results in Table 2), it can be established that the effects of the analyzed risk factors on the

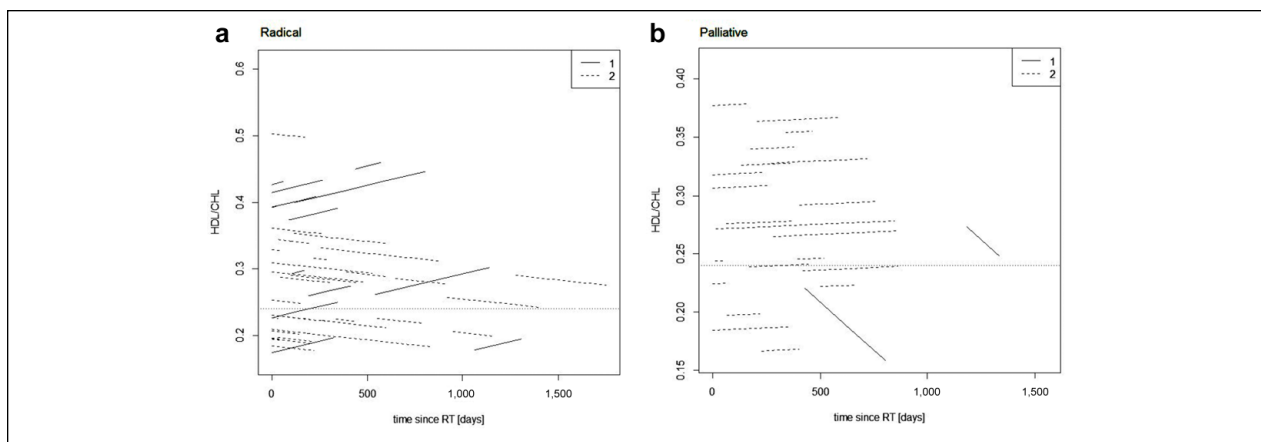


Figure 1. HDL/CHL ratio in patients vs. time and statin administration. (a) Radical treatment, (b) palliative treatment. 1— statin administration; 2—without statin. HDL = high-density lipoprotein; CHL = total cholesterol; RT = radiotherapy.

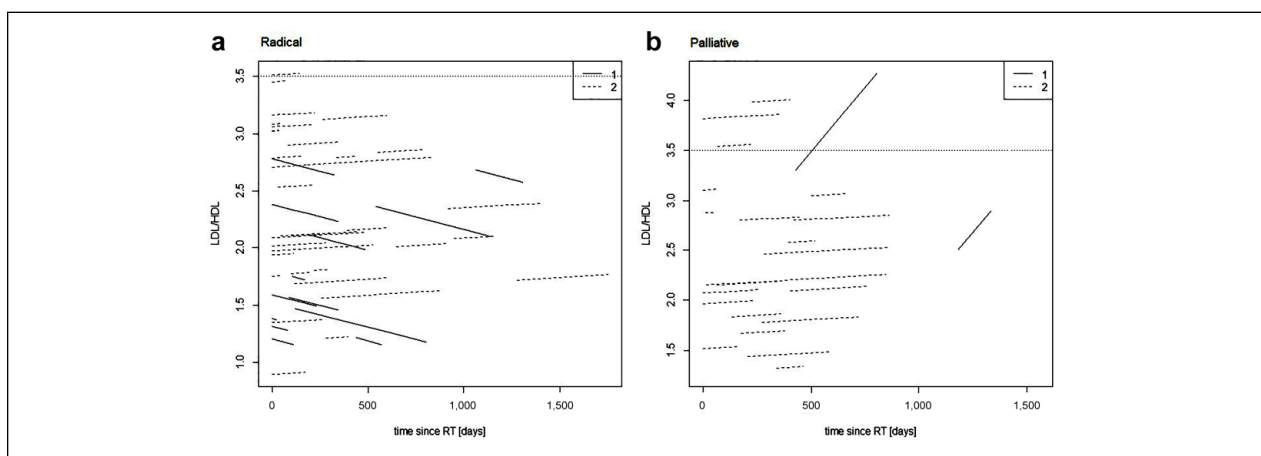


Figure 2. LDL/HDL ratio in patients vs. time and statin administration. (a) Radical treatment, (b) palliative treatment. 1— statin administration; 2—without statin. LDL = low-density lipoprotein; HDL = high-density lipoprotein; RT = radiotherapy.

TGL/HDL ratio, both in Group 1 and Group 2, were statistically random. All the HDL/CHL, LDL/HDL, and TGL/HDL ratios' linear trends described above, separately for Groups 1 and 2 subjects, are graphically plotted in Figures 1 to 3.

Discussion

Many studies describe and report a significant correlation between hypercholesterolemia or dyslipidemia and the incidence of prostate cancer (Ahn et al., 2009; Anand & Yusuf, 2011; Hayashi et al., 2012; Kitahara et al., 2011; Mondul, Clipp, Helzlsouer, & Platz, 2010; Moses et al., 2009; Platz et al., 2009; Van Hemelrijck et al., 2011). Cancer and the lipid profile have an inverse relationship and the possibility of prediction and the risk of cancer are still questionable (Bielecka-Dąbrowa, Hannam, Rysz, &

Banach, 2011). In the current study, serum HDL/CHL was increased in Group 1 compared to Group 2 ($p = .02$), and time–statin factor in relation was statistically significant ($p = .02$). For Group 2, this index decreased with each day after radiotherapy ($p = .07$), which means or could mean that the CHL was increased (suggesting a HDL/CHL index relationship). In a study of cervical cancer, Raju et al. (2014) described a similar statistically significant increase of CHL and LDL values, which were observed with the increase in disease stage. The serum TGs were significantly different between the cancer group and control group, but the change in lipid profile parameters in various grades was not statistically significant. In the current analysis, some of these lipid ratios, such as LDL and CHL, overlap with the values in that study, but the TGs were not significantly different. Moon et al. (2015) presented a thesis that a high level of CHL

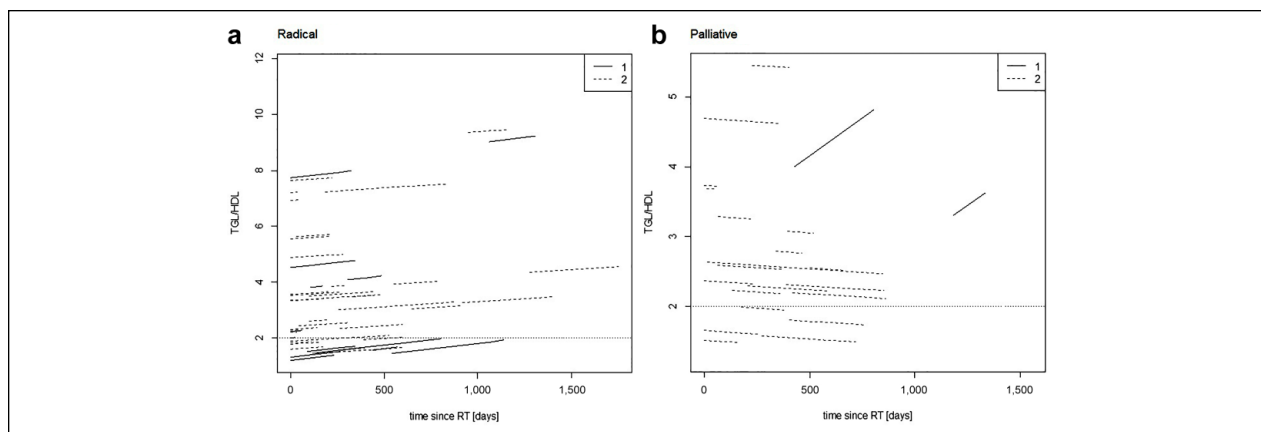


Figure 3. TGL/HDL ratio in patients versus time and statin administration. (a) Radical treatment, (b) palliative treatment. 1—statin administration; 2—without statin. TGL = triglyceride; HDL = high-density lipoprotein; RT = radiotherapy.

increases the size of the tumor and that “cholesterol acts as a magnet, attracting the protein to the tumor cell surface,” making it more aggressive. The same results were noted in the Group 2 subjects, which were on the border of statistical significance ($p = .07$). Palliative patients with advanced prostate cancer received ADT. The side effects of ADT were elevated lipid profiles and increased LDL cholesterol, HDL cholesterol, and TG (Saylor & Smith, 2013). A luteinizing hormone–releasing hormone (LHRH) analog altered serum lipoproteins in men with prostate cancer. In a study by Eri, Urdal, and Bechensteen (1995), mean CHL levels were significantly increased by 10.6%, HDL cholesterol was increased by 8.2%, and TG was increased by 26.9%, while LDL cholesterol levels remained unchanged. However, in Smith’s study, the serum CHL, HDL cholesterol, and LDL cholesterol increased significantly by 9.0%, 11.3%, and 7.3%, respectively. Serum TG also increased significantly by 26.5% (Eri et al., 1995; Smith et al., 2002). In the current study in Group 1, 70% of subjects received LHRH analogs and no statistically significant change in CHL was observed. A positive effect of time on the HDL/CHL ratio was noted. In turn, the LDL/HDL ratio was increased ($p = .04$) in subjects in Group 2. These results are similar to those of the McGrowder, Jackson, and Crawford (2012) study, which compared men undergoing long-term ADT with age-matched controls. Another author, Yuan et al. (2012), described increase in TG and decrease in HDL as significant at month 4 in the maximal androgen blockage group. In a retrospective cohort analysis of 843 radical prostatectomy (RP) subjects who had never used statins before surgery, Allott et al. (2014) demonstrated that elevated TG serum levels were associated with an increased risk of prostate cancer recurrence, but associations between CHL, LDL, and HDL and the recurrence risk were null. However, among men with dyslipidemia, each

10 mg/dL increase in CHL and HDL was associated with a 9% increase in recurrence risk (hazard ratio [HR], 1.09; 95% CI [1.01, 1.17]). The statins have an influence on cancerogenesis, lead to a decline of cancer cell migration, and slow down the cell cycle (Nielsen, Nordestgaard, & Bojesen, 2012). Statins inhibit the mevalonate pathway, which is regulated by the p53 positive feedback mechanism, which results in the reversal of the malignant phenotype of cells with mutant p53 (Nielsen et al., 2012; Sznarkowska, Olszewski, & Zawacka-Pankau, 2010). They also result in an increase in radiation sensitivity in cancer cells (Nielsen et al., 2012). In epidemiological studies, Solomon and Freeman (2008) described that statins inhibit the progression of cancer; however, in various reports, this effect on cancer is controversial. Authors Farwell et al. (2008) and Pelton, Freeman, and Solomon. (2012) reported that low plasma cholesterol levels are inversely correlated to the risk of prostate cancer, while the statin factor was positively associated with a decrease in cancer incidence. Similar conclusions were presented by Morote et al. (2014). They indicated that statins may prevent prostate cancer development by lowering cholesterol levels. In the current study, the decreasing effect of time and statin administration was noticed only in Group 1; in Group 2, this effect was borderline ($p = .06$). The analysis in the Danish national cancer registry reported that 15% less malignancy was diagnosed in patients treated with statins prior to diagnosis, irrespective of the dosage of statin administered (Nielsen et al., 2012).

Conclusions

The current study is limited because of the number of subjects and lack of homogeneity in both groups. In Group 1, there were different tumor stages and cancer advancement was limited to the prostate only. Group 2

consisted of subjects with metastases, both massive and solitary to the bones. This study only points out the problem and the clinical correlation between cancer and cholesterol and the role of using statins. As the survival rate of cancer subjects increases, control of the lipid profile gains importance.

Authors' Note

This manuscript has been approved by all authors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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