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The Effect of Radiotherapy on the Concentration of Plasma Lipids in Elderly Prostate Cancer Patients

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Abstract

Lipids play an important role in processes such as the formation of membrane cells or in steroidogenesis, where androgens which stimulate the proliferation of prostate cancer (PCa) cells are produced. Previous studies presented links between cholesterol (CHOL) and PCa and concluded that cholesterol homeostasis changes in PCa patients during treatment and with age. This study further examines the correlation between the lipid profile, the treatment used, and the subjects' age. Ninety-one subjects (Group 1: >69 years; Group 2: ≤69) histopathologically diagnosed with PCa were tested. Total CHOL, triglycerides (TG), high-density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) were assessed from blood taken before the entire course of radiotherapy (RT) and in 3-month intervals after the treatment was completed, for up to 4 years (range: palliative and radical). In all the subjects, the CHOL decreased over time after RT ($p = .0445$) with a simultaneous increase of prostate specific antigen (PSA) concentration ($p = .0366$). A faster decrease of HDL was observed with a higher concentration of PSA ($p = .0053$) and Gleason score ($p = .0304$). In all the subjects, the HDL decreased after RT ($p = .0159$) but in the older palliative group the HDL decrease progressed more slowly ($p = .0141$). It could be stated, that after radical therapy TG levels tended to be consistently higher among younger men relative to the elderly ($p = .0151$). But it was observed that RT treatment could lead to a decrease in the lipid serum concentration.

Keywords

elderly patients, cholesterol, prostate cancer, radiotherapy, triglycerides

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Lipids are organic compounds which may be divided into classes of biomolecules which ensure the proper metabolism and functioning of the organism. The major groups of lipoproteins in order of size are: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). They enable the transport of multiple different fat molecules, including cholesterol (CHOL). Any malfunctioning of the anabolic or catabolic processes of lipoproteins may lead to the development of pathological processes in cells. The disorders in lipid and lipoprotein metabolism can be a result of the metabolic syndrome—overweight and obesity—which can be associated with a higher risk of cancer and can have an impact on the prognosis in cancer patients (Hashmi et al., 2015; Huang & Freter, 2015; Riedel, Abel, Swanevelder, & Gelderblom, 2015). A lot of previous research (Jowett, 1931; White, 1909; Yasuda & Bloor, 1932) noticed that CHOL accumulates in malignant tissues. CHOL is the precursor in steroidogenesis (Murai, 2015) in which androgens are produced, which in

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turn stimulate the proliferation of prostate cancer (PCa) cells. Other authors point to the importance of factors such as a healthy endothelium and a very strong antioxidative system in cancer progression. LDL protects the endothelium against oxidation and oxidatively modified LDL is an atherogenic risk factor. LDL is also proven to downregulate lysyl oxidase (LOX), which is a kind of protein crucial in the cancer invasion. LOX bonds with pseudopods of cancer cells and allows them to pierce the basement membrane of vessels and thus contributes to the invasion and migration of cancer cells (Rodríguez, Raposo, Martínez-González, Casaní, & Badimon, 2002). If this LOX is downregulated, then the cancer cells cannot penetrate through the blood vessel and hence intravasation cannot take place. In the epidemiological studies (Anum & Adera, 2004), CHOL and LDL are reported to be significant risk factors in cardiovascular diseases, but with older age it changes and above the age of 70 these parameters are not risk factors any more. For men aged 80 years and above, the total CHOL identified an inverse relationship to mortality, that is, the subjects with low concentration levels of CHOL have a higher probability of death than subjects with a high concentration level of CHOL (diseases such as: cancer, infectious diseases, etc.,). The objective of this study was to investigate whether there is a similar connection between lipid profiles and age in PCa patients. Hence, in order to evaluate the changes of plasma lipid profiles and the clinical significance of these, the two groups of PCa patients were examined prior and after radiotherapy treatment (RT) treatment. There have been previous studies on lipid profiles in PCa patients but with treatment methods other than RT (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). The current study aimed to find connections between the factors such as age, cancer stage or treatment with regards to lipid profile. The examined hypothesis was that serum lipid levels could be potentially modifiable by RT and have some prognostic power.

Materials and Methods

Characteristics of Subjects

This is a retrospective study of 91 Caucasian men who were treated with external beam RT for PCa in Department of Radiotherapy of the Regional Clinical Hospital of Zielona Gora. This study was approved by the ethics committee at District Medical Council in Zielona Gora No 2/57/2012, and both oral and written consents were obtained from the subjects. The study was conducted by one physician over a period of 4 years between 2012 and 2016. The Eastern Cooperative Oncology Group (ECOG) scale was used and the subjects were classified according to the scale: 0–2. Blood samples were collected before RT (on the morning after fasting and before the initiation of androgen deprivation therapy [ADT]) and after the entire course of treatment in 3-month intervals for up to 4 years. The blood was evaluated with regards to lipid profile. The Roche Diagnostics GmbH Sandhofer Str.116 Mannheim Germany, Roche/Hitachi Cobas C Systems, and commercial kits were used to assess the lipid serum levels. The reference values for the normal ranges of the measured levels used by the Clinical Hospital of Zielona Gora are as follows: CHOL is 130–200 mg/dl, HDL are 35–80 mg/dl, LDL are 50–130 mg/dl, triglycerides (TG) are 65–150 mg/dl, and VLDL are 0–45 mg/dl. All subjects were clinically diagnosed with PCa and confirmed by a histopathological examination. The cases were placed into categories according to the TNM clinical stage (T–primary tumor site, N–regional lymph node, and M–metastatic spread) and divided into two groups of patients: Group 1—elderly subjects $>$69 years old and Group 2—subjects $\leq$69 years old. In Group 1, 40 men received treatment with radical prostate RT without nodal pelvis treatment, and 18 men received palliative RT (bone metastases RT without prostate RT). In Group 2, 21 men underwent radical prostate RT without nodal pelvis treatment, and 12 men had palliative RT (bone metastases RT without prostate RT). The locoregional subjects (48 patients –52% of the total numerous of patients) and metastatic PCa patients (30 patients – 33% of the total) obtained ADT treatment with the exception of 13 patients with Gleason score of $\leq$6 and prostate specific antigen (PSA) $<$10 ng/ml. Ten in Group 1 and 13 in Group 2 with hardness disease (bone pain and bone metastases) received bisphosphonates—zoledronic acid (ZA)-intravenous infusion every 21 days with check parameters such as calcium and creatine concentration levels. During the anamnesis, all subjects were asked about the duration of any treatment with statins, diabetes, and alcohol and nicotine use. Subjects qualified for the study did not have any aggravating factor like diabetes and restrained from alcohol and nicotine use during the treatment. Subjects' characteristics are summarized in Table 1.

Radiotherapy Treatment Used

Sixty subjects (those with metallic markers in the prostate gland) received radical RT treatment. The energy used over the course of treatment was as follows: a 6 MV and 15 MV photon beam for both intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) to the total dose of 76 Gy with 2 Gy per fraction, five consecutive days per week for the duration of 6–7 weeks; palliative subjects received 2D conformal

Table 1. Patients' Clinical Characteristics.

Feature:	Patients no 91 (100%)
Age:	72 (50–87)
Median (range)	
50–69	36 (40)
70–87	55 (60)
ECOG performance status:	
0	20 (22)
1	40 (44)
2	31 (34)
Histological diagnosis:	
Adenocarcinoma	91 (100)
Differentiation:	
Gleason score 2–6	36 (40)
Gleason score 7	24 (26)
Gleason score 8–10	31 (34)
Serum PSA ng/ml	
≤10	27 (30)
11–20	23 (25)
>20	41 (45)
Statins use:	*20 (22)*
ADT use:	*78 (85)*
Radiotherapy:	
Radical treatment total:	61 (67)
Group 1: >69 years	40
Group 2: ≤69 years	21
Palliative treatment total:	30 (33)
Group 1: >69 years	18
Group 2: ≤69 years	12

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

radiotherapy (CRT) with a conventional fractionalization of 4–8 Gy with the total dose of 6–20 Gy.

Statistical Analysis

This is a longitudinal study in which any changes of concentrations in the chosen biomarkers were examined for each participant over time—at 10 consecutive time points before and after RT treatment. Since a repeated measures' design was taken into account in this statistical analysis, a multilevel (hierarchical) modeling was applied. In particular, multilevel models are generalizations of linear models relying on nested random analysis of variance; they recognize the existence of data hierarchies by allowing for residual components at each level in the hierarchy (when a design includes both fixed and random effects, it is often called a mixed effects model). In the assumed concept, concentrations of the biomarkers with time and risk factors were analyzed using a stratified linear regression following a linear relation (concentration = time + risk factor), and the regression with an interaction term (concentration = time * risk factor; Raudenbush & Bryk, 2001). The following serum lipid concentrations (response variables) were modeled in the study: CHOL, HDL, LDL, VLDL, and TG. The selected available set of risk factors (explanatory variables) reported in Table 1 was used. In the analysis, only the statistically significant results of the stratified and interaction regression coefficients ($p < .05$) were considered. Results are reported in Table 2. Other relations of analyzed risk factors and lipid serum concentrations were statistically insignificant and were not presented in this article. Only one variable was considered significant in the statistical analysis and it concerned the patients' age with the cut-off point = 69 years. Lipid serum concentrations in patients' blood were measured before the RT treatment and after the completion of the whole course of treatment in up to eight consecutive follow-up visits every 3 months. The date gathered ranged from 100% to 3.3% completeness from first to eighth visit (from 17 to 1,837 days after treatment), with an average period between visits = 77 days. The statistical computation was performed in the MASS package (Package 'MASS', 2018) using the R platform (R Core Team, 2018).

Results

In this study, the correlations between the lipid profiles and the age of the subject post RT treatment were checked. It is of note, however, that most of the results were statistically significant for interaction regression. It means that the concentrations of the selected biomarkers change over time after RT, except TG, which is stratified (see Table 2 for details). Taking all the subjects into account, the results are as follows: the CHOL level decreased over time after RT ($p = .0445$) together with an increase in PSA concentration ($p = .0366$). The CHOL reduction was slower over time in patients with a higher PSA compared to those with a lower PSA concentration ($p = .0059$). A faster decrease of HDL was observed over time with a higher concentration of PSA ($p = .0053$) and a higher Gleason score ($p = .0304$). Contrary to HDL results, the higher concentration level of PSA accompany to slowly decrease of LDL over time. The ECOG status correlation with LDL ($p = .0688$) and combined with the presence of ZA did not lead to any significant changes of LDL over time ($p = .0823$). The treatment without the use of statins resulted in the slight increase of LDL ($p = .0079$) but without statistical significance over time. The VLDL was only statistically significant after RT in correlation with the ECOG status (the VLDL decreased with the increase of ECOG status [$p = .0455$]). The study showed that TG decreased after RT only in Group 1 ($p = .0196$), but over time is statistically insignificant ($p = .3156$). Finally, HDL was

Table 2. Multilevel Modeling of Biomarker Concentrations.

Study group	Response variable	Regression coefficient (risk factor)	Mean	*SE*	*p* value
All patients	VLDL	Intercept	30	6.0	<.0001
		ECOG	1.8	4.2	.6669
		Time	0.0098	0.0067	.1490
		ECOG*Time	−0.0098	0.0048	.0455
	HDL	Intercept	55	3.7	<.0001
		Gleason	−0.3642	1.5403	.8136
		Time	0.0055	0.0046	.2352
		Gleason*Time	−0.0049	0.0022	.0304
	CHOL	Intercept	198	5.0	<.0001
		PSA	−0.0470	0.0222	.0366
		Time	−0.0156	0.0077	.0445
		PSA*Time	0.00018	0.00007	.0059
	HDL	Intercept	54	2.1	<.0001
		PSA	0.0065	0.0088	.4593
		Time	−0.0002	0.0025	.9354
		PSA*Time	−0.00006	0.00002	.0053
	LDL	Intercept	115	4.5	<.0001
		PSA	−0.0144	0.0195	.4634
		Time	−0.0093	0.0070	.1864
		PSA*Time	0.00013	0.00006	.0314
	TG	Intercept	177	16	<.0001
		Age >69	−44	19	.0196
		Time	0.0189	0.0188	.3165
	HDL	Intercept	54	3.1	<.0001
		Age >69	−0.1223	3.9946	.9757
		Time	−0.0102	0.0041	.0140
		Age >69*Time	0.0103	0.0049	.0379
	LDL	Intercept	65	19	.0008
		Statins	28	10	.0079
		Time	0.0378	0.0279	.1775
		Statins*Time	−0.0239	0.0153	.1213
Radical	TG	Intercept	206	23	<.0001
		Age >69	−64.9	25.9	.0151
		Time	0.020	0.026	.4335
Palliative	HDL	Intercept	57	4.3	<.0001
		Age >69	−8.5	5.7	.1469
		Time	−0.022	0.009	.0159
		Age >69*Time	0.026	0.010	.0141

Note. ECOG = Eastern Cooperative Oncology Group; VLDL= very low density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins; CHOL = cholesterol; TG = triglycerides.

reduced with time ($p = .0140$); however, the decrease in the older group is smaller than in the younger group ($p = .0379$). With the division of the subjects into two groups according to their palliative and/or radical procedures, the concentrations of other lipids showed no statistically significant results. In all subjects, the HDL decreased after RT ($p = .0159$) but in the older palliative group, the HDL decrease happened at a slower pace ($p = .0141$). The only changes noticed after radical treatment were in the concentrations of TG (in Group 1, TG decreased after therapy [$p = .0151$]).

Discussion

After the radiation treatment, total CHOL and LDL among men with a more advanced disease (PSA, ECOG) decreased more slowly than among men with a less advanced disease. At the same time, HDL among those with a more advanced disease (PSA, Gleason score) decreased faster relative to those with a less aggressive disease. The treatment with the use of statins and ZA showed no significance with regards to lipid levels. After the radical RT treatment, the levels of TG in younger men was

higher than among the older ones and did not change over time. After the palliative RT in the older patients, HDL decreased faster. Moon et al. (2015) presented a thesis that a high level of CHOL increases the size of the tumor. This study shows that the CHOL decreases after RT but its reduction is slower in patients with a higher PSA compared to those with a lower PSA. This correlation is reversed between PSA and HDL levels—the decrease of HDL is faster in patients with a higher concentration of PSA and a higher Gleason score. Among the elderly men (>69 years), decrease of HDL is slower after treatment than in the group ≤69 years. Decrease of lipid levels in both groups is most likely due to the radiation. The metastases and advancement of diseases correlate with angiogenesis (a cancer growth and metastasis factor). In the studies of Raju et al. (2014) on cervical cancer and Ghahremanfard, Mirmohammadkhani, Shahnazari, Gholami, and Mehdizadeh (2015) on breast, colon, gastric, and ovarian cancers, it was observed that a statistically significant increase of CHOL and LDL values correlates with the advancement of the diseases. LDL is one of many factors that take part in the process of angiogenesis, which can inhibit this process. The growth of tumor and metastasis can be stopped by inhibiting angiogenesis (Vedavyas, 2013). In this study, decrease of LDL after treatment was shown and it was observed to be slower in higher concentration PSA and ECOG performance status. A borderline level decrease of LDL after RT was noticed when the treatment was combined with the use of bisphosphonates like ZA to reduce skeletal-related events (bone metastases). In literature, ZA has previously been shown to reduce levels of LDL (Gonnelli et al., 2014). This borderline result could be due to the small size of the subgroup treated with ZA. The role of statins as a preventative measure in the development of PCa as the factor which lowers CHOL levels is controversial. There are studies which report that statins inhibit the progression of cancer (Farwell et al., 2008; Morote et al., 2014; Pelton, Freeman, & Solomon, 2012; Solomon & Freeman, 2008; Wolny-Rokicka, Tukiendorf, Wydmański, & Zembroń-Łacny, 2017). In this study, the treatment without statins resulted in the increase of LDL but without statistical significance over time. PCa patients often display significantly lower levels of serum cholesterol (Bielecka-Dąbrowa, Hannam, Rysz, & Banach, 2011; Munir et al., 2014) but it is questionable whether these factors may be used to predict the risk of cancer. In the study by Allott et al. (2014), elevated serum TG levels were associated with an increased risk of PCa recurrence. In Hayashi et al.'s (2012) study, the authors emphasized the same trend of increased TG levels together with a higher Gleason score ≥8 in elderly patients as a factor in PCa recurrence. In the current study, RT was a chosen method of treatment and proved to show a statistically significant association between TG and time. Over the course the RT and afterwards, in patients >69 years a decrees of TG levels was noticed. The limitations of this study include the relatively low number of subjects and the lack of homogeneity in both groups.

Conclusions

This study described changes in blood lipid profiles among middle-aged and elderly men with PCa after RT. Changes in lipid levels are differentially affected by various other factors such as somatic disease—neurological, cardiac, and gastrointestinal somatic symptoms. This study only examines the clinical correlation between RT and its effect on the lipid profile in elderly patients. In order to properly evaluate this "effect," a broader group of subjects would be needed with the adjustment for confounding factors including ADT, ZA, statins, type of RT, disease severity, diabetes, BMI, and so forth. It was observed that RT treatment could lead to a decrease in lipid serum concentration. A broader study could further prove this.

Declaration of Conflicting Interests

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