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| RESEARCH ARTICLE

Association of Prostate Cancer and Lipid Profile: A Case-Control Study

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| ABSTRACT

There are inconsistent findings concerning the association between the serum concentrations of lipid parameters and prostate cancer (PCa), particularly in Caucasian men. There is limited data on men of African ancestry. The study examined the relationship between serum total cholesterol (TC) levels and its fractions and PCa in a hospital-based case-control study in Jamaica. The serum levels of TC, triglycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) in 46 male patients (cases) who underwent prostate biopsy were measured over an eighteen month period. There were 32 patients without PCa who served as controls. The serum lipid concentrations between cases and controls were compared using an independent samples t-test. Multiple linear regression and binary logistic regression were used to assess the relationship between lipids and overall PCa, as well as disease severity. Based on the results, there were no significant differences between the concentrations of lipids for the cases and controls. The results of the regression analysis revealed that the serum lipid levels were not significant predicators of overall PCa. The outcomes of the binary regression analysis showed the same for PCa severity. The study concluded that there was no association between serum levels of lipids and overall PCa as well as disease severity at the time of diagnosis in the sample of Jamaican men.

| KEYWORDS

Lipids, prostate cáncer, disease, severity, association, case, controls

| ARTICLE INFORMATION

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1. Introduction

Prostate cancer (PCa), the most frequently diagnosed solid malignancy in Jamaican men, is the chief cause of cancer mortality (16.5% of total cancer deaths) (Blake et al., 2002). Researchers in Jamaica reported age-standardized PCa incidence rates of 56.4 and 65.6 per 100,000, respectively, over consecutive 4-year periods (1993 to 1997 and 1998 to 2002) using data from the largely urban-based Jamaica Cancer Registry (Hanchard et al., 2001; Gibson et al., 2008). Another study reported an age-standardized PCa incidence rate of 78.1 per 100,000 over the 4-year period 2003-2007 (Gibson et al., 2010).

Cholesterol comprises approximately 33% of the plasma membrane, and there is evidence that as a biomolecule, it is involved in the initiation, growth, and aggression of PCa through its action on steroidogenesis and the inflammatory process within prostate cells (Cruz et al., 2013; Zadra et al., 2013). There are experimental studies that attest to the role of cholesterol as a substrate for cellular androgen biosynthesis (Green et al., 2012), abnormities in its metabolism, and subsequent tumor development in mouse models (Masko et al., 2017).

Clinical studies have shown contradictory findings where elevated serum total cholesterol (TC) levels were related to advanced PCa (Shafique et al., 2012; Jamnagerwalla et al., 2018) and higher risk of overall PCa by some researchers (Kok et al., 2011; Platz et al., 2008), while others reported a relationship between low TC levels and elevated risk of disease (Heir et al., 2016). Furthermore, similar findings of associated higher PCa risk were stated for raised serum low-density lipoprotein-cholesterol (LDL-C) (Farwell et al., 2011) and triglycerides (TG) levels (Mondul et al., 2011) but lower disease risk for increased serum high-density lipoprotein-cholesterol (HDL-C) levels (Van Hemelrijck et al., 2011).

A meta-analysis of fourteen prospective studies of Caucasians in 2015 by Liu YuPeng and colleagues established no relationship between PCa risk and advanced disease and serum levels of the components of the lipid panel (TC, TG, LDL-C, and HDL-C) (YuPeng et al., 2015). However, there is limited data on overall and high-grade PCa, and lipid profiles in persons of African ancestry, principally those living in the Caribbean.

This study examined the relationship between serum TC levels and its fractions (TG, HDL-C, and HDL-C) and PCa (overall and disease severity) in a hospital-based case-control study in Jamaica.

2. Materials and Methods

2.1 Selection of Cases and Controls

Men, 46-91 years old, attending the University Hospital of the West Indies (UHWI) Urology Clinics in Kingston, Jamaica, were recruited to a case-control study over an eighteen-month period. The UHWI Urology Clinics receive referrals from primary care clinics, hospitals, and private practitioners island-wide; most patients reside in the Kingston Metropolitan areas. The majority of referrals were for patients with complications of benign prostatic hyperplasia (BPH), suspected cases of PCa, and urinary tract stones. To a lesser extent, patients are referred for investigation and treatment of other suspected genitourinary malignancies or disorders (e.g., male-factor infertility and erectile dysfunction).

Prostate biopsy was used to confirm PCa, and histologic grade was reported using the Gleason system (Epstein et al., 2016). All positively diagnosed cases were reviewed by a single Anatomical Pathologist who has had additional training in grading using this grading system. The clinical staging of PCa was determined by the urologists. Controls were cancer-free subjects attending the UHWI Urology Clinics who underwent a prostate biopsy due to suspicion of PCa. Participants in the control group had a negative digital rectal examination (DRE) result.

The study received approval from The University of the West Indies/University Hospital of the West Indies (UHWI/UWI) Faculty of Medical Sciences Ethics Committee. All patients involved in the study gave written informed consent.

The following persons were excluded from the investigation: (i) men with previous prostate surgery, (ii) on hormonal treatment, and (iii) patients with a history of diabetes mellitus or other neurological lesions.

2.2 Biochemical analysis

After a 12-hour overnight fast venous blood sampling was performed, blood was collected from the patients, and measurement of serum lipid concentrations was conducted on the same day that the patients underwent prostate biopsy. Blood samples were allowed to clot for 30 minutes, centrifuged at 3,500 rpm for 5 minutes, and the serum was aliquoted. Serum total prostate specific antigen (tPSA) levels were measured at the Chemical Pathology Laboratory, UWI using a micro-particle enzyme immunoassay method (Dasgupta et al., 2000).

Biochemical assays of lipid parameters in the serum samples were performed with a multichannel auto analyzer (c8000, Abbott Diagnostics, Abbott Park, USA). Serum TC and HDL-C levels were determined by enzymatic methods (Allain et al., 1974; Burstein et al., 1970). Serum TG levels were determined by an analytical methodology (Fossati and Prencipe, 1982), and LDL-C levels were calculated using the Friedewald equation (Friedewald et al., 1972).

Normal reference values of the constituents of the lipid profile were adopted according to the guidelines of the US National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III, 2001). The values of TC and its fractions, TG, LDL-C, and HDL-C, which are categorized as a normal reference, optimal, borderline high, and very high, can be found in a previous publication (Gordon et al., 2012).

2.3 Lipid Variables

The study investigated any association between men with higher TC (> 5.18 mmol/L), TG (> 1.70 mmol/L), HDL-C (> 1.04 mmol/L), LDL-C levels (> 2.59 mmol/L), and overall PCa, as well as disease severity [high-grade (Gleason score ≥ 7) or low-grade (Gleason score < 7)]. Categorical lipid variables were generated as follows: (i) patients with total cholesterol levels less than 5.18 mmol/L

were classified as having "Low Cholesterol," and those with levels equal to and greater than 5.18 mmol/L were classified as "High Cholesterol" (ii) patients with triglyceride values less than 1.70 mmol/L were classified as having "Low Triglycerides" and those with levels equal to and greater than 1.70 mmol/L classified as "High Triglycerides", (iii) patients with HDL-cholesterol levels less than 1.04 mmol/L were classified as having "Low HDL-C " and those with levels equal to and greater than 1.04 mmol/L classified as "High HDL-C" and (iv) patients with LDL-cholesterol levels less than 2.59 mmol/L were classified as having "Low LDL-C " and those with levels equal to or greater than 2.59 mmol/L classified as "High LDL-C".

A PCa severity categorical variable was generated. Patients who were found with Gleason score less than 7 were classified as having "Low grade," and those with Gleason score equal to or greater than 7 were classified as "High Grade."

2.4 Statistical Analysis

The results are expressed as mean ± standard error (S.E.). Multiple linear regression and binary logistic regression were used to assess the relationship between TC, TG, HDL-C, LDL-C, and overall PCa. Also, in the determination of multivariable odds ratio (ORs) and 95% confidence intervals (95% CI) of the total high-grade (Gleason score ≥ 7) and low-grade (Gleason score < 7) disease, conditional logistic regression was utilized.

The Skewness Kurtosis test was conducted to determine if the distribution of the following variables was normally distributed. The independent samples t-test was used to determine if there were any differences in the following lipids: TC, TG, HDL-C, and LDL-C by group (operationalized as cases and controls).

3. Results

Of the 78 subjects, 46 were diagnosed with PCa, and 32 were controls. In the 46 cases, the mean age was 67.04 ± 1.88 years, with most in the age group 60 - 69, while for the controls, the mean age was 67.00 ± 3.10 years.

The mean value of tPSA in cases (87.35 ± 29.56 ng/mL) was markedly elevated compared with controls (9.95 ± 3.00 ng/mL). The mean values of serum TC and LDL-C levels (4.39 ± 0.16 mmol/L and 2.75 ± 0.14 mmol/L, respectively) in cases were not significantly less when compared with controls (4.68 ± 0.14 mmol/L and 2.99 ± 0.13 mmol/L) (**Table 1**).

The mean values of serum TG and HDL-C levels (1.18 ± 0.12 mmol/L and 1.10 ± 0.05 mmol/L, respectively) in cases were not significantly different from the controls (1.15 ± 0.09 mmol/L; P = 0.8825 and 1.14 ± 0.06 mmol/L respectively) (**Table 1**).

The percentage of cases with serum TC levels within normal limits (< 5.18 mmol/L) was 71.7% which was not different from controls (75.0%). Also, similar results were observed for TG, LDL-C, and HDL-C (**Table 2**).

The results of the regression analysis revealed that serum TC, TG, HDL-C, and LDL-C levels were not significant predicators of overall PCa. It is noted that high serum HDL-C levels were near borderline significant (P = 0.069) (**Table 3**). Likewise, the results of the binary regression analysis revealed that serum TC, TG, HDL-C, and LDL-C levels were not significant predicator of the PCa severity (**Table 4**).

4. Discussion

The results of our study demonstrated that serum TC, TG, LDL-C, and HDL-C levels were similar in controls and PCa patients. The findings also revealed that these lipid parameters were not significant predicators of overall PCa or disease severity. Similar to ours, a case-control study conducted by Jackson and colleagues examined the association between serum TC levels and PCa in men of African descent and found that the same did not differ between cases and controls and was unrelated to overall PCa. Likewise, serum HDL-C levels were not significantly associated with overall PCa, although higher levels of serum TC were significantly related to an elevated risk of low-grade disease (Tulloch-Reid et al., 2017). In a later cohort study of 1,314 cases of Caucasian men who underwent radical prostatectomy, Rantaniemi and colleagues found no association between serum TC levels and PCa severity (Rantaniemi et al., 2018). There are a few other studies that have corroborated our findings (West et al., 1991; Kolonel et al., 1988; Arthur et al., 2016), but others have reported that high levels of TC and TG may impact PCa severity and aggressiveness (Arthur et al., 2016; Platz et al., 2009; Morote et al., 2014). Moreover, in a hospital-based case-control study of Caucasian men, hypercholesterolemia was significantly associated with PCa risk at diagnosis, and the same was shown for low HDL-C (Magura et al., 2008). This was not in keeping with the findings of our study, in which no association was observed between elevated lipids levels and overall PCa in men of African descent. In another study involving Puerto Rican men, elevated serum TG and low HDL-C levels were significantly associated with high-grade PCa. However, in the same study, serum TC levels were not related to PCa severity (Salgado-Montilla et al., 2015). On the contrary, TC and LDL-C levels were significantly reduced in PCa patients, and low levels of these parameters were associated with overall PCa (Garrido et al., 2021). Notably, there were no significant differences in TG and HDL-C levels between cases and controls, a finding that is in agreement with that of our study (Garrido et al., 2021).

There is evidence; however, that is supportive of the possible involvement of lipid metabolism in the development of PCa (Van Hemelrijck et al., 2011). Cholesterol possesses pro-cancer properties. It is intricately involved in pathways relating to inflammation, cellular multiplication, and steroidogenesis, and its metabolism is reprogrammed in PCa (Murtola et al., 2012). Extra free cholesterol is stored as cholesteryl esters, and elevated levels have been shown to be associated with PI3K/Akt activation, tumor progression, and metastatic PCa (Yue et al., 2014). Moreover, LDL-C may participate in prostate oncogenesis and severity, and increased levels were related to higher PCa risk in African American men compared with their Caucasian counterparts (Moses et al., 2009).

Our study has a few limitations, including the small number of subjects in both groups. The variables in this study were not adjusted for statin or other lipid-lowering drug usages, alcohol use, family history of PCa, and smoking behavior. Furthermore, an assessment of other lifestyle practices could not be conducted as this is not a prospective or longitudinal study. Nonetheless, the limitations enacted by sample size and this case-control study reveal the possible relationship between lipid parameters and PCa in an understudied population with high PCa incidence and mortality rates.

5. Conclusion

Our study examined the association between serum TC levels and its fractions with the overall disease severity of PCa in a hospital-based case-control study in Jamaica. The results of our study suggest no association between serum lipids with overall PCa and disease severity. As such, our study provides further evidence of no link between lipid parameters and PCa in men of African descent on disease diagnosis. The limitation of our study consists of the fact that it was conducted in a single center with a relatively small number of participants. This warrants further studies with a larger number of men with confirmed PCa to better ascertain the role of serum lipids in PCa development, especially in this understudied population.

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Table 1: Lipid parameters of patients with prostate cancer and controls.

Lipid Parameters	Patients with Prostate Cancer	Controls	P-Value
	Mean ± S.E.	Mean ± S.E.	
Total Cholesterol *	4.389 ± 0.162	4.678 ± 0.136	0.2040
Triglycerides (mmol/L)	1.175 ± 0.121	1.151 ± 0.092	0.8825
HDL-cholesterol (mmol/L)	1.095 ± 0.049	1.141 ± 0.061	0.5543
LDL-cholesterol (mmol/L)	2.749 ± 0.142	2.985 ± 0.133	0.2503
TC/HDL-cholesterol ratio	4.599 ± 0.375	4.472 ± 0.278	0.8021

*Total cholesterol (mmol/L)

Table 2: Classification of lipid parameters of controls and prostate cáncer patients according to NCEP ATP III

	Prostate Cancer Group	***Control Group***
Lipid parameters	**Number (%)**	**Number (%)**
Total cholesterol		
Low cholesterol	33 (71.7)	24 (75.0)
High cholesterol	13 (28.3)	8 (25.0)
Triglyceride		
Low triglycerides	41 (89.1)	27 (84.4)
High triglycerides	5 (10.9)	5 (15.6)
HDL-cholesterol		
Low HDL-cholesterol	20 (43.5)	13 (40.6)
High HDL-cholesterol	26 (56.5)	19 (59.4)
LDL-cholesterol		
Low LDL-cholesterol	23 (50.0)	
High LDL-cholesterol	23 (50.0)	9 (28.1)
		23 (71.9)

Table 3: Relationship between lipid parameters and prognosis of overall prostate cancer

Outcome: Gleason score	Coefficient (CI)	P
Cholesterol category Low Cholesterol level	Reference	
High Cholesterol level	0.047 (-0.62-0.71)	0.886
Triglycerides category Low Triglyceride level	Reference	
High Triglyceride level	-0.36 (-1.27-0.54)	0.426
HDL-cholesterol category High HDL-cholesterol level	Reference	
Low HDL-cholesterol level	-0.48 (-0.99-0.03)	0.069
LDL-cholesterol category Low LDL-cholesterol level	Reference	
High LDL-cholesterol level	-0.12 (-0.72-0.47)	0.679

Table 4: Relationship between lipid parameters and prostate cancer severity

Outcome: Gleason Score category	OR (CI)	P
Cholesterol category Low Cholesterol level	Reference	
High Cholesterol level	1.55 (-00.25-0.83)	0.641
Triglycerides category Low Triglyceride level	Reference	
High Triglyceride level	0.26 (0.02-3.06)	0.282
HDL-cholesterol category High HDL-cholesterol level	Reference	
Low HDL-cholesterol level	0.39 (0.086-1.83)	0.238
LDL-cholesterol category Low LDL-cholesterol level	Reference	
High LDL-cholesterol level	0.70 (0.14-3.59)	0.671