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Altered Levels of Blood Glucose and Serum Lipids in Sudanese Patients with Ovarian Cancer

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Abstract

Background: The etiology of ovarian cancer is not well-understood; numerous metabolomics profiling, epidemiological, and hospital-based case control studies have associated abnormal levels of blood glucose and serum lipids with the risk and the prognosis of various types of cancers including ovarian cancer. The association between the risk of the incidence of ovarian cancer and the alterations in the levels of blood glucose and serum lipids is not well defined. **Objective:** In this study we aimed to compare the levels of blood glucose, triacylglycerols, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in patients with different stages of ovarian cancer and healthy controls to determine how they relate to the risk and prognosis of ovarian cancer. **Methodology:** In a case-control cross sectional study, we enrolled ninety-nine Sudanese women, diagnosed with ovarian cancer but had not received any kind of treatment as the study group, and a control group of forty-one age-matched, apparently healthy women. The patients were classified according to the International Federation of Obstetricians and Gynecologists staging system into two groups: early stages (stage I & II) and late stages (stages III & IV). Blood glucose and serum lipids; triacylglycerols, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were determined by enzymatic colorimetric methods using commercially available analytical kits. The IBM SPSS version 20 software was used for statistical analysis. A Mann-Whitney U test was used for comparison of the median concentrations of blood glucose, triacylglycerols, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol in the study groups. Logistic regression model was used to estimate the relative risk of ovarian cancer in relation to levels of blood glucose

and serum lipids. *P* value of 0.05 was considered significant. **Results:** Our data indicated significantly higher levels of blood glucose ($p < 0.001$), triacylglycerols ($p = 0.002$), and low-density lipoprotein cholesterol ($p < 0.001$), and lower levels of high-density lipoprotein cholesterol ($p = 0.023$), in ovarian cancer patients compared to the control subjects. No significant difference was found in the levels of blood glucose or any of the serum lipids between patients in the early stages (stage I & II) and those in late stages (stage III & IV) of ovarian cancer. The logistic regression analysis indicated significant association between the elevated levels of the blood glucose, triacylglycerols and low-density lipoprotein cholesterol and the risk of the ovarian cancer. **Conclusion:** We conclude that the levels of blood glucose, triacylglycerols, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol differ significantly between ovarian cancer patients and the healthy control subjects. The risk of ovarian cancer was positively associated with the levels of blood glucose, triacylglycerols and low-density lipoprotein cholesterol, and negatively associated with levels of high-density lipoprotein cholesterol. Therefore, determination of blood glucose and serum lipids, particularly, triacylglycerols, low-density lipoprotein cholesterol may be helpful as diagnostic indicators of ovarian cancer (OC).

Keywords

1. Introduction

Ovarian cancer (OC) is insidious and accounts for the most gynecological cancer deaths, with a global incidence and mortality rates of 6.6 and 4.2 per 100,000 population respectively [1]. Because of the delayed onset of symptoms and a lack of effective early detection or prevention methods, OC is often diagnosed at late stages with a poor prognosis and high mortality rate. In Sudan, data from hospital registries, national diagnostic and academic centers, as well as from the population-based national cancer registry, rank OC as the third most common gynecological cancer, accounting for 6.4% of the total malignancies among Sudanese women with an incidence rate of 8.0 per 100,000 population [2] [3].

Although the etiology of OC is not well-understood, research indicates that several factors including genetic, family history of breast or ovarian cancer, environmental factors, dietary habits, and certain lifestyle factors increase the risk of the disease, while grand multiparity, breastfeeding, use of contraceptives, and salpingo-oophorectomy are believed to reduce the risk [4]. Apart from the identified risk factors, numerous metabolomics profiling, epidemiological, and hospital-based case control studies have associated abnormal levels of blood glucose and serum lipids with the risk of various types of cancers including OC [5]-[16]. Although these studies have so far linked altered levels of BG and serum lipids to the risk and severity of the OC, their results were mostly conflicting, and the re-

lationship between the levels of BG, and serum lipids and the risk of OC remained equivocal. For example, a number of studies found significantly higher levels of TAGs in patients with OC [5] [6] [12] [13] [16] [17] [18], while another study has reported low levels of TAGs in OC [9]. Likewise, there are reports of low levels of circulating TC in OC patients compared to healthy controls [8] [10] [13] [14] [15], and other reports of moderate or high levels of TC in OC patients compared to healthy control [12] [19]. Similarly, analysis of the levels of LDL-c and HDL-c in patients with OC have shown contradicting results [9] [12] [13] [18]. Moreover, studies investigating the association of serum lipids with the risk, or prognosis of ovarian cancer [6] [11] [17] [20] have also produced conflicting data. While some of those studies have shown positive associations between elevated levels of BG or serum lipids and the risk or prognosis of OC, others indicated negative associations [6] [11] [17] [20]. Considering these previous reports, several inconsistencies can easily be noticed, indicating a need for further research to clarify the nature of the association between the BG, serum lipid components, and the risk and prognosis of OC. In this study, we aimed to compare the levels of BG and serum lipids in patients with different stages of OC and healthy controls to determine how they relate to the risk and prognosis of OC. The study hypothesis was that abnormal levels of BG or serum lipids are associated with the incidence and severity of OC.

2. Materials and Methods

2.1. The Study Population

This is a case-control cross sectional study which is conducted in the period between September 2013 and March 2015. In this study, we enrolled ninety-nine Sudanese women, diagnosed with ovarian cancer but had not received any kind of chemotherapeutic treatment. Clinical diagnosis of ovarian cancer was made by oncologists in the Radiation Isotopes Center in Khartoum (RICK) according to the standard protocol adopted by the Sudanese Ministry of Health. The diagnostic protocol included complete abdominal and pelvic examination, abdominal and transvaginal ultrasound followed by surgery and collection of specimens from the ovarian mass. Based on clinical data and the operative report, each case of ovarian cancer was staged according to the International Federation of Obstetricians and Gynecologists staging system (FIGO) [21]. Forty-one, age-matched women were enrolled as a control group. The control subjects were selected mostly from relatives who attended as co-patients, they were apparently healthy and do not complain of any chronic disease.

After informed consent, demographic and clinical data of patients and control subjects was collected in a questionnaire designed for this purpose. Five ml of venous blood were collected in lithium heparin tubes from each participant in the morning after 12 hours of fasting for measurement of BG and serum lipids. The blood specimens were immediately centrifuged at 3000 rpm for 15 minutes, and the sera were collected in aliquots for subsequent determination of the levels

of BG and serum lipids.

2.2. Laboratory Procedures

Commercially available, Biosystem kits were used for determination of serum BG, TAGs, TC, LDL-c and HDL-c according to the manufacturer's procedures. Briefly, BG was assayed by Trinder method, which is an enzymatic colorimetric method using glucose oxidase to produce gluconic acid and H_2O_2. In the presence of the peroxidase, phenol, the chromogenic 4-aminoantipyrine form the red-colored quinonimine dye [22]. The intensity of the color, which is proportional to the glucose concentration, is determined by measuring the absorbance at 510 nm, and the glucose concentration is determined against standard control.

Triacylglycerols level was assayed using an enzymatic method described by Buccolo and David [23], in which TAGs is enzymatically hydrolyzed by lipase to yield free fatty acids and glycerol, the latter is then phosphorylated by glycerol kinase to form glycerol-1-phosphate which in turn is oxidized to dihydroxyacetone phosphate and H_2O_2. Then a series of reactions in the presence of peroxidase, 4-aminoantipyrine and sodium *N*-ethyl-*N*-(3-sulfopropyl) *m*-anisidine produce quinonimine dye with a color intensity directly proportional to TAGs concentration in the specimen. The color absorbance was measured at 540 nm, and the TAG concentration is determined against standard control.

The TC assay was performed by a colorimetric method as described by Allain *et al.*, [24] in which cholesterol esters are hydrolyzed to free cholesterol by cholesterol ester hydrolase. The free cholesterol produced is oxidized by cholesterol oxidase to cholest-4-en-3-one with the simultaneous production of H_2O_2, which in the presence of peroxidase, phenol and the chromogenic 4-aminoantipyrine system forms the red-colored quinonimine dye with maximum absorbance at 500-550 nm. The method for determination of HDL-c depends on the presence of a detergent which solubilizes only the HDL so that the HDL-c is released to react with the cholesterol esterase, and the cholesterol released is them determined in steps similar to the one described above for measurement of TC.

The LDL-cholesterol is calculated from measured values of TC, TAGs and HDL-c according to Friedewald equation; [LDL-c] = [TC] − [(HDL-c) + (TAG)/5], where TAG/5 is an estimate of VLDL-c and all values are expressed in mg/dL [25].

2.3. Statistical Analysis

Data was analyzed using the IBM SPSS version 20.0 (IBM SPSS, New York. USA) statistical Package. The demographic variables related to age and BMI were compared by student *t*-test. The biochemical parameters which were not normally distributed were expressed as Median (25th and 75th Percentiles). Mann-Whitney U-test for comparison of median was used to compare the levels TC, TAGs, LDL-c, and HDL-c. Two-tailed *p* value ≤ 0.05 was considered significant. Logistic regression was performed to determine whether BG or any com-

ponent of the serum lipid is significantly associated with the risk of ovarian cancer.

3. Results

3.1. Comparison of the Age, BMI, Blood Glucose and Serum Lipids in Patients and Healthy Control Subjects

The mean age of the entire study group was 53.3 years (range, 25 - 75). The patients and control groups were of similar age, the mean and standard error of age of the patient's group was 52.1 ± 0.12 year and for the control group were 53.8 ± 0.13 year. Out of the 99 patients, 33 (33.3%) were in stage I, 30 (30.3%) in stage II, 26 (26.3%) in stage III, and only 10 (10.1%) were in stage IV. The patients have significantly lower BMI (22.6 ± 0.7) compared to the control subjects (26.7 ± 0.7), *t*-test (3.4, *p* = 0.001). Table 1 shows the median, 25th and 75th percentiles for the BG, TC, TAGs, LDL-c, and HDL-c. Mann-Whitney U test showed significantly higher levels of BG, TAGs, LDL-c, and lower levels of HDL-c in patients compared to the control subjects.

3.2. The Comparison of the Levels of the Blood Glucose and Serum Lipids between Early and Advanced Stage Patients

Table 2 shows the comparisons of the levels of BG, TC, TAGs, LDL-c, HDL-c between the early stages (stage I and II) and the advanced stages (stages III and IV) OC patients. No significant difference is detected in any of these biochemical

Table 1. Blood levels of blood glucose and serum lipids in OC Patients and healthy control subjects.

Parameter	Median (25th and 75th Percentiles)		Mann-Whitney U Test (Sig)
	Patients N = 99)	Controls (N = 41)	
BG, mg/dL	108.5 (100 - 124)	93 (79 - 100)	0.000*
TC, mg/dL	164 (144 - 221)	179.3 (147 - 200)	0.527
TAGs, mg/dL	162 (119.5 - 222.4)	121 (112 - 150)	0.002*
LDL-c mg/dL	114 (76.1 - 152)	110 (52 - 88)	0.000*
HDL-c mg/dL	45.7 (28 - 54)	52.2 (38 - 75)	0.023*

Table 2. Blood glucose and serum lipids in early and late stages OC patients.

Parameter	Median (25th and 75th Percentiles)		Mann-Whitney U Test (Sig)
	Early stages patients (N = 33)	Late stages Patients (N = 51)	
BG, mg/dL	107(90 - 124)	112 (83 - 128)	0.702
TC, mg/dL	163 (146.5 - 223.1)	164 (143.9 - 216)	0.442
TAGs, mg/dL	160 (131- 217)	187 (112 - 240)	0.409
LDL-c mg/dL	114 (76.1 - 144.7)	110 (76.1 - 152)	0.716
HDL-c mg/dL	47.3 (40.0 - 61)	43.6 (31.3 - 64)	0.510

parameters between the patients in early stages and those in the late stages of the disease.

3.3. The Logistic Regression for Association of the Incidence of OC and the Biochemical Parameters

A logistic regression was performed to ascertain the effects of BG, TAGs, TC, LDL-c, HDL-c on the likelihood that participants have ovarian cancer. Table 3 shows the logistic regression model which included in addition to the above-mentioned parameters the age and the BMI. The model was statistically significant, χ^2 (3) = 62.9, $p < 0.001$, and explained 52.0% (Nagelkerke R^2) of the variance in ovarian cancer and correctly classified 81.2% of cases. Increased levels of BG, TAGs, and LDL-c were significantly associated with an increased likelihood of exhibiting ovarian cancer.

Table 3. The logistic regression for the effect of BG, TG, and LDL-c, on risk of ovarian cancer

Parameter	B	S.E.	Wald	Sig.	Odd ratio	95.0% C.I. for EXP (B)	
						Lower	Upper
BG	0.034	0.013	6.989	0.008*	1.035	1.009	1.061
TAGs	0.016	0.006	8.324	0.004*	1.016	1.005	1.027
LDL-c	0.020	0.005	18.756	0.000*	1.020	1.011	1.029
Constant	−7.007	1.556	20.271	0.000*	0.001		

4. Discussion

Cancers cause marked alterations in almost every aspect of glucose and lipid metabolism [26]. So far, several researches have associated altered levels of BG and serum lipids and the risk or severity of OC [5] [6] [8] [10] [11] [17] [19] [27] [28]. However, the exact nature of the association remained controversial. Our study results have shown significantly higher levels of BG, TAGs, LDL-c and low HDL-c in the OC patients compared to the control group. These findings confirm previous reports [5] [6] [12] [18] [28] [29] [30], but contradict others who reported significantly lower levels of TAGs or LDL-c in OC patients compared to healthy controls [9] [13]. Interestingly, our findings with regard to serum lipids concord with results of a recent metabolomic analysis intended to predict the biomarkers of OC prognosis, in which increased levels of TAGs were identified as a characteristic biomarker of serum lipid profile in OC patients [29].

Our finding of significantly low levels of HDL-c in patients compared to healthy controls is not surprising, as previous reports including a recent meta-analysis, have indicated similar findings [10] [30] [31]. Although we found a low but not significantly different levels of TC in the OC patients compared to the healthy controls, however, this finding agrees with the results reported by several other authors [8] [10] [13] [15] [9] [27]. Conversely, other researchers

have reported moderate or high increase in the levels of TC in OC patients compared to healthy control [12] [19] [30]. However, this contradiction could be attributed to sample size or differences in research design.

The logistic regression analysis in this study indicated that increased levels of BG, TAGs and LDL-c are associated with an increased risk of OC. These findings confirm results of previous studies that have significantly associated elevated serum levels of TAGs and LDL-c with the risk, severity and prognosis of OC [5] [6] [11] [17]. However, other authors have reported that OC patients with elevated LDL-c were showing shorter survival compared to those with elevated LDL-c [32], while elsewhere, low levels of LDL-c were associated with the risk of recurrence of OC [33]. With regard to the HDL-c, previous studies, including two meta-analysis, have associated the low levels of HDL-c with increased risk or severity of the OC [6] [34] [35] [36]. In line with these, our results indicate that low HDL-c levels correlate with a high risk of OC.

5. Conclusion

We conclude that levels of BG, TAGs, LDL-c and HDL-c differ significantly between OC patients and the healthy control subjects. The risk of OC was found to be positively associated with the levels of TAGs and LDL-c and negatively associated with the levels of HDL-c. No significant differences were found in the levels of these biochemical parameters between patients in early stages compared to those in the late stage of the disease. Therefore, determination of BG and serum lipids, particularly, TAGs, LDL-c and HDL-c, may be helpful as diagnostic indicators of OC. Further studies are required to characterize the pathophysiologic mechanisms implicated in the alterations of the serum lipid profile during progress of the OC.

6. Limitations

Although the whole sample size of OC patients was sufficiently large, the sample size for the separate subgroups of the different disease stages was not sufficiently large to enable the determination of the difference between the various disease stages.

Acknowledgements

Ethical Considerations

The study has been approved by relevant ethical review committees in the University of Kordofan and the RICK. All participants have provided written informed consent.

Authors' Contribution

Hassaan M.A. planned the study, collected the samples, and conducted the laboratory analysis.

Khirelsied A.H. analyzed the data and contributed to the manuscript writing.

Ali T.M. contributed to the manuscript writing and revision.

Agab-Aldour A.A. contributed to the research design and supervised the conduction of the study and laboratory work. All authors have read and agreed to the submitted version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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