Original Article

Lipid profiles of Sudanese cancer patients

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Abstract

Objectives
There is increasing evidence that cancer cells show specific alterations in different aspects of lipid metabolism. These alterations can affect the availability of structural lipids for the synthesis of membranes, the synthesis and degradation of lipids that contribute to energy homeostasis and the abundance of lipids with signaling functions. This study assessed the changes in plasma lipids levels in cancer patients prior to treatment at the National Cancer Institute - University of Gezira (NCI-UG) in Sudan.

Patients and Methods
A total of one hundred participants were enrolled into this study: fifty patients with different types and clinical stages of cancer; in addition to fifty healthy volunteers were included as a control group. The standard enzymatic colorimetric method was used for measuring the levels of triglycerides, total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and albumin.

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Results
The levels of HDL-C and albumin were significantly decreased in cancer patients compared to the control group ($P= 0.0002$ and $P=0.0009$, respectively). The LDL-C level was significantly increased in patients with BMI $\leq 25$ ($P = 0.03$). However, no significant differences were found in the levels of the total cholesterol and triglycerides between the two groups.

Conclusion
The results of this study suggest that alterations in HDL-C and LDL-C are associated with cancer and can be used in approaches to diagnostic, preventive and therapeutic interventions in cancer patients.

Keywords: lipid profiles, cancer, Sudan

Introduction
Cancer is a leading cause of death globally. The World Health Organization (WHO) estimates that 7.6 million people died of cancer in 2005 and 84 million people will die in the next 10 years if action is not taken. By 2015, that number is expected to rise to 9 million and increase further to 11.5 million in 2030. More than 70% of all cancer deaths occur in low- and middle-income countries, where resources available for prevention, diagnosis and treatment of cancer are limited or nonexistent. Cancer cells are characterized by diminished or unrestrained control of growth, invasion of local tissues, and spread or metastasis to other parts of the body. Several metabolic changes have been detected at the surface of malignant cells: alteration of permeability, alteration of surface charge, alteration of the activities of a number of enzymes (e.g. certain proteases), change of glycolipid constituents, and alteration of oligosaccharide chains of glycoproteins. It is also noted that cancer cells have specific alterations in lipid metabolism. Cholesterol is necessary for the growth and proliferation of cancer cells. Moreover, mevalonic acid, a precursor of cholesterol, plays an essential role in deoxyribonucleic acid replication. Mevalonate in early $G_1$ in cell cycle presumably provides structural cholesterol, which permits the cell to pass through $G_1$ and reach the S phase of the cell cycle. Most enzymes involved in fatty-acid and cholesterol biosynthesis are regulated by the sterol regulatory element-binding proteins (SREBPs), mutant tumor protein p53 associates with SREBP at the promoters of genes within the mevalonate pathway and increases their expression. Up-regulation of lipogenic enzymes and elevated lipogenesis has been shown to occur in many cancers. Thus, increased fatty acid synthesis may even be required for carcinogenesis and has been linked to other cancer associated metabolic changes. The aims of this study were to investigate whether cancer is associated with lipids and lipoproteins abnormalities and whether the pattern of lipid abnormalities is linked to disease stages and nutritional status.

Patients & Methods
This case-control study included 50 newly diagnosed untreated patients (18 men and 32 women) attending the National Cancer Institute, University of Gezira (NCI-UG), Sudan. Diagnosis of all cases was confirmed histopathologically and blood samples were collected prior to treatment. All patients with diseases that affect lipid digestion and/or metabolism (hypothyroidism, obstructive liver disease, pancreatic diseases, kidney diseases, hypertension or cardiovascular diseases) were excluded. For comparative analysis, a control group was recruited including 50 healthy Sudanese adults (18 men and 32 women). The mean age of the cancer patients group was 47.44 ± 16.50 years (range, 19 - 90 years) whereas the mean age of the control group was 42.64 ± 16.11 years (range, 19 - 80 years). A venous blood sample was obtained from the patients and controls in the fasting state, i.e. at least 12 hours after their last meal. The serum concentrations of total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides, and albumin were measured.
(LDL-C), triglyceride (TG) and albumin were measured by a standard colorimetric method using MITRA-SN No.801630176 spectrophotometer instrument and kits from BioSystems S.A., Barcelona, Spain. Statistical analysis was performed using Graphpad prism version 4.03 for Windows (Graphpad Software, San Diego California USA, www.graphpad.com). P values ≤ 0.05 were considered significant.

Results
Serum levels of albumin, TG, TC, HDL-C, and LDL-C in the cancer patients and controls are summarized in Table 1 as mean ± SD. The mean value of albumin was 3.71 ± 0.60 (g/l) for cancer patients and it was significantly lower than the corresponding mean value (4.08 ± 0.47) of the control group (P=0.0009). Mean levels of TG, TC and LDL-C levels were not significantly different between the two groups; whereas the HDL-C level was significantly lower in the cancer patients (46.93 ± 15.87) compared with corresponding mean value of 58.71 ± 14.27 in the control group (P=0.0002).

Table 1: The measurements of serum albumin and lipid parameters in cancer patients and controls (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer pts. (n = 50)</th>
<th>Controls (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>3.71 ± 0.60</td>
<td>4.08 ± 0.47</td>
<td>0.0009</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>78.08 ± 39.17</td>
<td>76.17 ± 30.72</td>
<td>0.7862</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>159.76 ± 50.05</td>
<td>159.91 ± 29.35</td>
<td>0.9854</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>68.05 ± 41.08</td>
<td>58.44 ± 29.25</td>
<td>0.1808</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>46.93 ± 15.87</td>
<td>58.71 ± 14.27</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Moreover, comparison of lipid parameters between patients and control group with BMI ≤ 25 have shown a statistically significant decrease in albumin and HDL-C and increase in LDL-C (P=0.02, P=0.0005 and P=0.03 respectively) as presented in Table 2.

Table 2: Comparison of lipid parameters between the cancer patients and controls with BMI 25 or less (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer pts. (n = 35)</th>
<th>Controls (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>3.72 ± 0.58</td>
<td>4.04 ± 0.51</td>
<td>0.0256</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>77.92 ± 41.08</td>
<td>69.71 ± 23.77</td>
<td>0.3387</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>165.00 ± 53.54</td>
<td>153.40 ± 28.78</td>
<td>0.283</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>71.06 ± 44.52</td>
<td>50.96 ± 25.02</td>
<td>0.0321</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>46.54 ± 15.8</td>
<td>60.32 ± 14.20</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

The frequency distribution of different cancer types is shown in Fig 1. The selected biochemical parameters were compared in the five frequent cancer types (gastrointestinal, breast, head and neck, urogenital, and hematological cancers) and controls (Table 3); Overall significant differences were found between groups in the mean concentrations of albumin (P= 0.0210) and HDL-C (P= 0.0003). For HDL-C, the most prominent decrease was found in the head and neck cancers as well as hematological cancers.

Comparisons between the mean concentrations of albumin and lipid parameters in the patients grouped according to disease stage and the control group are presented in Table 4. There was an overall significant decrease in the levels of albumin (P= 0.04) as well HDL-C levels (P= 0.001) in subgroups of different cancer stages compared to the control group; the decreases in the levels of albumin and HDL-C were most evident in patients with stage III and IV. No significant differences were detected in the levels of TG, TC and LDL-C.
Table 3: Comparison of the selected biochemical parameters in the subgroups of the 5 common types of cancer and the control group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastrointestinal (n=12)</th>
<th>Breast (n=10)</th>
<th>Head and Neck (n=9)</th>
<th>Urogenital (n=9)</th>
<th>Hematological (n=4)</th>
<th>Controls (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>3.59±0.59</td>
<td>3.80±0.48</td>
<td>3.62±0.96</td>
<td>3.81±0.44</td>
<td>3.50 ± 0.65</td>
<td>4.08 ± 0.47</td>
<td>0.0210</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>91.02±57.31</td>
<td>78.03±28.69</td>
<td>68.77±34.37</td>
<td>69.48±19.57</td>
<td>102.83 ± 62.11</td>
<td>76.17 ±30.72</td>
<td>0.4587</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>159.43±37.72</td>
<td>178.14±41.58</td>
<td>140.17±61.99</td>
<td>186±67±46.15</td>
<td>122.45 ±63.76</td>
<td>159.91 ± 29.35</td>
<td>0.2899</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>58.97±37.48</td>
<td>81.36±50.62</td>
<td>65.60±39.34</td>
<td>78.29±35.53</td>
<td>35.46±44.05</td>
<td>58.44 ± 29.25</td>
<td>0.1728</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>51.57±19.04</td>
<td>56.56±16.53</td>
<td>34.94±11.02</td>
<td>49.52±9.15</td>
<td>38.35±17.04</td>
<td>58.71 ± 14.27</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Table 4: Comparison of the estimated biochemical parameters in different stages of cancer (mean± SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage I (n=3)</th>
<th>Stage II (n=9)</th>
<th>Stage III (n=22)</th>
<th>Stage IV (n=10)</th>
<th>Controls (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>3.57±1.19</td>
<td>3.90±0.43</td>
<td>3.71±0.61</td>
<td>3.73±0.58</td>
<td>4.08±0.47</td>
<td>0.04</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>112.70±69.25</td>
<td>73.09±54.69</td>
<td>77.70±29.46</td>
<td>67.09±17.99</td>
<td>76.17±30.72</td>
<td>0.37</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>187.70±66.67</td>
<td>176.50±17.50</td>
<td>159.60±63.07</td>
<td>140.10±34.55</td>
<td>159.91±29.35</td>
<td>0.27</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>90.67±54.15</td>
<td>68.59±38.46</td>
<td>69.00±45.70</td>
<td>67.08±27.74</td>
<td>58.44±29.25</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>39.40±18.45</td>
<td>53.94±7.88</td>
<td>44.98±17.21</td>
<td>44.72±14.48</td>
<td>58.71±14.27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion
Under-nutrition status (assessed by BMI) in the cancer patients was observed in the majority of patient, with statistically significant decreased in serum albumin level that correlated with advanced stages III and IV. This result could be explained by that cancer cells depend on the body nutrients for their growth and blood supply, and that the growing tumor has high metabolic rate and may deprive the body of nutrients\(^8\). Increase in the whole body protein turnover and subsequent loss of body nitrogen have been reported in 50-70% of cancer patients\(^9\). It was documented that low serum albumin concentration predicts a poor prognosis in cancer patients\(^10\). A previous study in ovarian cancer showed that there was a direct correlation between serum albumin levels and survival, patients with lower levels having poor survival\(^11\).

This study provides evidence that low serum HDL-C is associated with stage of cancer where its level was significantly reduced among cancer patients. Low HDL-C was significantly associated with stage III and IV. The function of HDL–C is reverse cholesterol transport. The pleiotropic properties of the HDL-C particle including its anti-oxidative function, modulation of cytokine production, blockage of apoptosis and stimulation of cell proliferation and migration, are more likely to play a role in the development of cancer\(^12\).

Our results appear consistent with the findings of Anchisi and his group, that the cancer patients are characterized by lower levels of HDL-C. Human neoplastic cells have active proteolytic enzymes on the external surface of the cells, lead to degradation of protein component of HDL\(^13\), It was also reported that certain tumor tissues have a higher receptor- mediated uptake of lipoproteins\(^14,15\).

Previous studies have separately shown alterations in the plasma levels of lipids, lipoproteins and apolipoproteins reflecting patients' pathologic conditions and may indicate a poor prognosis\(^16\). Our results in agreement with the findings of Halton et al\(^17\) in acute lymphocytic leukemia that children with widespread disease had lower concentrations of cholesterol and HDL-C than...
children with localized tumors. A significant decrease in HDL-C and total cholesterol was revealed by Patel et al.\(^{(18)}\) in head and neck cancer patients and this was linked to increased utilization by neoplastic cells for biogenesis of new membranes. Studies on breast cancer, showed that low HDL-C among premenopausal women may be a marker of increased breast cancer risk.\(^{(13)}\) Examining the association of total cholesterol, HDL-C and LDL-C with progressive stage IV breast cancer, significant decreased levels were observed.\(^{(19)}\) Alteration in lipid profile levels showed a significant correlation with breast cancer risk, disease status and treatment outcome.\(^{(20)}\)

Although, serum HDL-C has been recognized as a better marker of metabolic status than total serum cholesterol, a complete standard lipid profiles have been conducted in many studies. In our study, the total cholesterol and triglyceride levels were not significantly different between cancer patients and controls, this may be due to inclusion of different cancer types and small sample size. This result seems inconsistent with observations of low cholesterol in patients with breast tumor,\(^{(20)}\) head and neck cancer,\(^{(18)}\) and hepatocellular carcinoma.\(^{(16)}\) On the other hand, other investigators found elevation of total cholesterol.\(^{(21,22)}\) Additionally, triglycerides level was found to be high in acute lymphocytic leukemia,\(^{(17)}\) and breast cancer.\(^{(21)}\)

Sub-grouping study participants according to BMI, the LDL-C level was significantly increased (\(P=0.03\)) among cancer patients with BMI of 25 or less (Table 2). Interestingly most of patients in this group were in stage III and IV (17 patients in stage III and 7 patients in stage IV). This result is in accordance with Notarnicola et al study\(^{(22)}\) who illustrated that high serum lipid levels may facilitate the development of distant metastasis. It was suggested that the elevated plasma LDL-C concentration, which is more susceptible to oxidation, may result in higher lipid peroxidation in breast cancer patients, that may cause oxidative stress leading to cellular and molecular damage thereby resulting in cell proliferation and malignant conversions.\(^{(21)}\)

In males with colorectal cancer the high LDL-C and low HDL-C levels were linked to lymph node metastasis.\(^{(23)}\) The uptake of LDL by its receptor (LDLR) provides cells with essential fatty acid for prostaglandin E\(_2\) (PGE\(_2\)) synthesis, which subsequently stimulate cell growth.\(^{(15)}\) Recently, it was suggested that both HDL and LDL could be used as carriers to conjugate water-insoluble anti-cancer drugs, which improve drug efficacy through direct or indirect tumor targeting, increased bioavailability and diminished toxicity.\(^{(24,25)}\)

Our data culminate that, in the patients’ group the levels of albumin and HDL-C were significantly decreased, while the LDL-C level was significantly increased and related to the advanced stages of cancer. However, the total cholesterol and triglycerides levels were not significantly different between the two groups. Thus, the alterations in the levels of albumin and lipoproteins might be considered among prognostic markers. The current study highlights the significance of assessing these biomedical markers in cancer and a possible involvement in developing cardiovascular problems in cancer patients. In settings with limited resources, albumin and lipid profiles could be used as potential markers for disease progression and clinical outcome.

References
2. WHO. The World Health Organization's Fight Against Cancer: strategies that