Original Article

New diagnostic markers in basal cell carcinoma

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Abstract

Background: The clinical significance of plasma lipoprotein levels in the diagnosis and prognosis of certain diseases is known fact. Some studies have reported different and contradictory levels of blood lipoproteins in cancer patients. Therefore, we decided to compare lipid profiles in patients with basal cell carcinoma (BCC) and healthy individuals.

Materials and Methods: In this case-control study, lipid biomarkers in blood plasma of 64 patients with BCC compared with biomarkers in 64 healthy subjects. According to including criteria's both group selected. 5 cc blood samples taken after 8–12 h of fasting. Ultimately, the diagnosis of biopsy samples confirmed by the dermatopathologist. The information data entered into the PASS II software and then characterized by a descriptive and analytical statistics of the lipid profile. The role of the related factors was assessed by two sample *t*-test power analysis.

Results: In this research, mean age of patient group and the healthy one was 67.13 ± 11.33 and 64.31 ± 6.98, respectively. The average amount of triglyceride, cholesterol, high density lipoprotein (HDL) and low density lipoprotein in the BCC patients were 147.97 ± 87.11 mg/dl, 188.25 ± 38.90 mg/dl, 61.98 ± 18.61 mg/dl and 95.98 ± 31.69 mg/dl, respectively, whereas these amounts in the control group were 137.34 ± 61.41 mg/dl, 173.22 ± 38.79 mg/dl, 42.34 ± 7.83 mg/dl and 106.44 ± 35.17 mg/dl, respectively. There were statistically significant differences between cholesterol and HDL in patients with BCC and healthy controls, respectively ($P = 0.030$) ($P < 0.001$).

Conclusion: It seems that changes in lipid profile can help as a diagnostic marker for detecting cancer like BCC. Although this change could be different in lipid markers and also among different types of cancer.

Keywords: Basal cell carcinoma, blood lipoprotein, lipid profile

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer in humans which is accounts 75%–80% of skin cancers. The history of sunburn and chronic sunlight exposure plays a critical role in increasing the incidence of this cancer. In addition to ultraviolet (UV) radiation, which is a major risk factor in the development of skin cancers, other etiologic and known risk factors such as lymphoma/leukemia, AIDS and other disorders and immunological diseases, radiotherapy, X-rays, arsenic poisoning, human papillomavirus infection and etc., can be identified.[1] Meanwhile, changes in lipid profile and serum lipoproteins which are associated with some skin cancers, including BCC, have been reported.[1,2] Lipid profiles are a series of blood tests that are used

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as an initial screening tool to diagnose abnormal lipid conditions in patients. Lipid profiles measure the levels of cholesterol and triglycerides (TGs) in serum or plasma, which can be used to detect some of the genetic diseases and identify the risk of cardiovascular disease. Generally, lipid profiles include low density lipoprotein (LDL), high density lipoprotein (HDL), TGs and total cholesterol (TC). Other values such as LDL (VLDL), as well as other profile ratios such as cholesterol/HDL, can be calculated with the availability of the basic profile values.[3,4] Lipids are the main components of cell membranes and play a role in various biological applications such as inflammatory responses, cell integrity, cell growth and cell division both in normal and malignant tissues. Cholesterol is a structural member of the cell membrane and is effective in the transmission paths of the message. Many of these pathways are linked to their effect on the formation of cytoskeletal structures, cell polarity and angiogenesis with malignancy and cancerous conditions. Cholesterol is also a steroid hormone that has been shown to play the role in cancers such as breast cancer. In particular, the diagnostic value of LDL in breast cancer has been determined.[5] Many studies have been conducted on the association of lipids and lipoproteins with the risk of developing various cancers, and for some lipids, there has been a direct and for others, a reverse relationship has been reported.[6,7] Meanwhile, the association between lipids biomarkers in serum and plasma with BCC, has contradictory results, suggesting that the mechanism of lipid metabolism in BCC is still unclear and requires more extensive examination.[8,9]

For example, a study has shown that serum levels of LDL, TG and serum cholesterol in patients affected by BCC were not significantly different from the control group,[9] While another study suggested that patients with BCC have higher regional and serum lipids than healthy people.[2] In recent years, the discovery of molecular markers has been emphasized, and body fluids such as saliva, blood and urine have been used for early diagnosis, prognosis and monitoring of disease progression. The use of blood and blood tests for ease of use, economic benefits and repeatability to conduct research is more favorable. Therefore, the aim of this study was to evaluate and comparison of the levels of TC, LDL, HDL and TG in BCC patients and healthy controls, which can be a potential diagnostic and prognostic tool.

MATERIALS AND METHODS

This case–control study will be performed on the blood of 64 patients with BCC and 64 healthy people. The case group is randomly selected from patients referring to the Razi Hospital. The including criteria's for case group, were no history of obesity, alcohol consumption, diabetes, Cushing's syndrome and long-term use of corticosteroids and effective drugs at lipid levels such as corticosteroid and estrogen. The control group also selected from healthy adults without a history of skin cancer and criteria's similar to those for the case group. The two groups were matched for age and sex. After explaining the purpose of the study and completing the consent form, a physical examination was performed by a dermatologist and personal information such as age, sex, location of the lesion and eventually the histopathologic type of the tumor was recorded in the designed information form. It is worth mentioning that blood test/taking blood from patients routinely is performed before surgery according to routine surgical treatment for patients with BCC in the hospital (5 cc blood samples taken after 8–12 h of fasting). The obtained lipid profile values are recorded in the information form. The natural range of serum lipids is as follows: TG <200 mg/dl; CHOL <200 mg/dl; HDL >35 mg/dl; LDL <130 mg/dl. Ultimately, the diagnosis of biopsy samples confirmed by the dermatopathologist (if the tumor diagnosis was not confirmed, the sample excluded from the study). In the case of healthy people, by referring to the laboratory of the same hospital, people who have been referred for the usual check-up and blood tests containing these markers logged from the laboratory's archives. The information form data entered into the PASS II software and then characterized by a descriptive and analytical statistics of the lipid profile. The role of the related factors judged by two sample *t*-test power analysis.[1,10]

RESULTS

This study was performed on 128 individuals, 64 of whom had BCC and 64 were healthy. Of these, 82 (64.1%) were male and 46 (35.9%) were female. The mean age of the total population was 65.72 ± 9.49 years. The mean of TGs value in patients with BCC was 147.97 ± 87.117 and its mean in healthy people was 137.34 ± 61.418. The mean of cholesterol value in patients with BCC was 188.25 ± 38.902 and its mean in healthy people was 173.22 ± 38.798. The mean of HDL value in patients with BCC was 61.98 ± 18.618 and its mean in healthy people was 42.34 ± 7.832. The mean of LDL value in patients with BCC was 95.98 ± 31.691and its mean in healthy people was 106.44 ± 35.178.

The mean of TGs in patients with BCC is higher than healthy controls. However, the results of Mann–Whitey U-test showed that this difference was not statistically significant ($P = 0.968$).

The mean of cholesterol in patients with BCC was more than healthy subjects, which was statistically significant ($P = 0.030$). Furthermore, the studies showed that mean cholesterol in men with BCC was significantly higher than healthy men ($P = 0.024$).

The mean HDL in patients with BCC was more than healthy controls. The results of Mann–Whitney U-test showed that this difference was statistically significant ($P < 0.001$). Similarly, mean HDL in men and women with BCC is more than healthy controls. The results of Mann–Whitney U-test showed that these differences were statistically significant (both case $P < 0.001$).

The mean LDL is higher in healthy controls than in patients with BCC. The results of independent samples *t*-test showed that this difference was not statistically significant ($P = 0.080$).

DISCUSSION

As mentioned in the findings, the mean age of BCC was in the 7th decade of life which is in line with this epidemiologic finding based on the age of BCC involvement that is in the fourth decade or more. In the present study, sexual frequency in bcc and healthy controls showed that the number of male patients in BCC group was higher than female patients, but this difference was not statistically significant ($P = 0.048$).

In this study, the level of lipid markers which measured in patients with BCC were TG: 147.97 ± 87.11 mg/dl, Chol: 188.25 ± 38.90 mg/dl, HDL: 61.98 ± 18.61 mg/dl and LDL: 95.98 ± 31.69 mg/dl. In the control group, the level of lipid markers was TG: 137.34 ± 61.41 mg/dl, Chol: 173.22 ± 38.79 mg/dl, HDL: 42.34 ± 7.83 mg/dl and LDL: 106.44 ± 35.17 mg/dl.

However, in the study of Zamanian *et al*.,[1] the lipid markers in BCC individuals were TG: 139.73 ± 69.11 mg/dl, Chol: 179.20 ± 43.42 mg/dl, HDL: 39.40 ± 9.30 mg/dl and LDL: 110.70 ± 34.13 mg/dl and in healthy controls were TG: 141.83 ± 80.41 mg/dl, Chol: 173.60 ± 96.32 mg/dl, HDL: 36.97 ± 6.35 mg/dl and LDL: 104.87 ± 30.85 mg/d.

In contrast to our study, findings in Zamanian *et al*.'s[1] study showed that serum lipid levels in patients with BCC has no significant difference in comparison with the healthy group ($P > 0.05$). Furthermore, in his study stated that lipid profiles increased in patients with cancer although this increase had been negligible. However, they believed that change in the levels of these markers could serve as an indicator for identifying early changes in the process of cancer formation.[1] It should be noted that small sample size in his study could be a reason for this contradiction.

Similarly, and in line with the results obtained in our study, in the study of Vural *et al*.,[9] there was a significant increase in all lipid profile values in the patient population compared to healthy controls.[9]

In a study by Que *et al*.,[11] the importance of evaluating these markers in cancer patients has been mentioned, and it has been argued that abnormal lipid profiles can contribute to the onset and progression of cancer. They said "a decreased HDL-cholesterol (HDL-C) level was significantly associated with decreased overall survival" in patients with soft tissue sarcomas.[11]

In a study by Chi *et al*.,[10] reviewing all lipid markers in 228 patients with lung cancer, the results showed that all markers except TG in cancer patients were decreased, but increased levels of TG were observed in these patients. The study also noted that reducing HDL levels in patients will be accompanied by a reduction in survival rates.[10] Their results contradicted our findings, which may reflect the different markers' effects and roles among different cancers.

In a study by Kamath *et al*.,[12] who looked at lipid markers in oral cancer patients, the results were relatively similar to those of our study. In this way, all lipid markers except HDL increased in patients with oral cancer, although there was no statistically significant difference. However, in the case of HDL, the findings showed that the level of this marker in patients was significantly reduced compared with the control group, and this decrease was statistically significant.[12] It seems that this difference in the reduction of HDL in people with oral cancer (squamous cell carcinoma) is due to differences in the demographic characteristics of patients and the differences in the type of cancer examined. As noted in the literature, SCC has differences in etiology, mechanism of development and metastasis compared to BCC.[9]

In a study by Naik *et al*.,[13] who evaluated plasma lipid profile patterns in oral leukoplakia (OL) and oral SCC, Plasma TC was reduced and LDL was increased in individuals with OL and OSCC ($P > 0.05$). HDL, VLDL, TG were reduced significantly in OL and OSCC individuals and more so in OSCC individuals ($P < 0.001$). The important point was that among the OL group, speckled leukoplakia had the lowest lipid profile levels and verrucous group has maximum level of TC and LDL ($P < 0.05$).

Furthermore, the level of VLDL in the leukoplakia group with dysplasia was lowest than the level in cases having no dysplasia ($P < 0.05$).[13] Finally, they founded reduced lipid profile in OSCC and OL cases. A significant inverse association between lipid levels and OSCC like many other studies which controverts with our finding. They stated that "Even lipid profiles can be used as a marker for malignant transformation in cases of OL". Therefore, early detection of malignancies in OL and early treatment can be possible, which leads to increase the survival rate in these patients.[13]

Cholesterol and TGs are the important lipid constituents of the cell and are essential to carry out several vital physiological processes. In malignancies, the blood cholesterol undergoes early and significant changes. Low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the process of carcinogenesis.[13] Patel *et al*.,[14] reported that oral precancerous lesions and conditions in general are associated with reduced lipid profile. Low levels of cholesterol have been associated with increased incidence of cancer and the reverse also has been true where in cancers are associated with low levels of cholesterol. In the previous article stated that lowered lipid profile could assess the prognosis in patients with OSCC since less of cholesterol in cellular membrane makes the cells hyperpermeable. This permeability results in the carcinogens reach nucleus more easily and causes DNA alteration and cause of malignancy. Furthermore, defect in cholesterol synthesis results in T and B lymphocyte impairment functions, and after that loss of immune surveillance which results in identifying the cancer cells with problems.[13] In that study, it has been reported that smoking alters the serum lipid and lipoproteins by elevation of serum free fatty acids after smoking. Of course our study did not investigate this factors and its effect on lipid profile.

Findings in some epidemiologic studies consistent with our findings, suggest a positive association between elevated serum cholesterol level and risk for certain cancer types such as prostate cancer. Surprisingly, an equal number of epidemiologic studies suggest no association between cholesterol and cancer, unlike controlled experiments in mice that showed an association between dietary cholesterol and cancer. So, preclinical studies tend to be more helpful for identifying role of dietary cholesterol in cancer development because multiple mechanisms promoting deregulation of cholesterol homeostasis identified that could lead to cancer development. Recent studies also suggest that intracellular cholesterol levels might be more important than serum cholesterol in the development of cancer. Furthermore, intracellular cholesterol homeostasis varies among different cancer types and therefore could play differing roles dependent on cancer type. Cholesterol is an essential lipid for maintaining cellular homeostasis and also plays a key role in intracellular signal transduction. In melanoma, one of the skin cancer, increased activity of the cholesterol synthesis pathway was correlated with decreased patient survival while in tumor such a lower grade glioma it was associated with enhanced survival. Thus, there appears to be a correlative link between cholesterol synthesis pathway and prognostic outcome that could be cancer-type specific. Several oncogenic signals, such as PI3K/AKT/mTOR, RTK/RAS and TP53, have been shown to modulate cholesterol synthesis in cancer cells. For example; Studies in cultured cells suggested that induction of cholesterol synthesis by the AKT/mTORC1/SREBP pathway contributed to cell growth. But, in glioblastoma, expression of LDL receptors was induced by AKT and pharmacologic targeting of LDL receptors effectively promoted tumor cell death.

Also, TP53 is the most frequently mutated gene that deregulating the cholesterol pathway in cancer and is a poor prognostic indicator. It identified that, loss of TP53 function unregulated the cholesterol synthesis pathway in breast cancers. As a key tumor suppressor for a wide variety of cancers, TP53-mediated modulation of cholesterol homeostasis could contribute to the progression of other malignancies, which requires further investigation. In the other hand, in several cancer types, elevated mitochondrial cholesterol levels induced resistance to apoptotic signals. Altered expression levels and mutations of genes involved in the cholesterol homeostasis pathways have been identified in cancer cells. Hence, it appears that variant changes in cholesterol homeostasis could be seen in different types of cancers that leads to different effect on cancer development.[15]

In a study by Chandler *et al*.,[5] there was a significant association between colon cancer and HDL values as same as findings identified in our research that demonstrated a significant association between BCC and HDL values. However, contrary to the findings of these two researches, the study of Laisupasin *et al*.[16] has shown that HDL levels in the patients group did not significantly increase compared to the healthy group.

On the other hand, Patel *et al*.[14] reported that Chol and HDL levels were significantly lower in the patients with head and neck cancer than the control group. These results are in contradiction with the findings from our study; it seems that maybe the difference in the types of cancer between these two studies seems to justifying this contradiction. In this study, in order to justify this reduction

in lipid profile level, stated that cancer cells will use an increased amount of lipids for the biogenesis of the new membrane, the phenomenon that leads to reduction in their levels.

In a study by Mehta *et al*.,[17] who examined lipid profiles in equally patients with precancerous and cancerous oral lesions and healthy individuals, a significant decrease in lipid markers in precancerous and cancer patients compared to healthy controls was observed. Furthermore, this decrease was significantly noticeable in the cancer patients than in the case of precancerous lesions. This researcher and his colleagues stated that changes in lipid levels could have a diagnostic and prognostic role in precancerous and cancerous lesions. Thus, they suggested with this change in lipid levels, careful examination of the precancerous lesions should be made.

The influence of cholesterol on cancer risk has been an area of investigation for long-time. Many studies and meta-analyses had separately reported this factor as an important etiologic factor for the development and progression of certain types of cancer. In recent years high lipid profile marker such as serum cholesterol has been linked to the development of cancer although the results are inconsistent. Some underlying mechanisms have been proposed.[18]

Blood lipids and lipoproteins may influence carcinogenesis through insulin resistance, inflammation and oxidative stress pathways.[19]

Lipids are the major cell membrane components essential for various biological functions and Cholesterol may cause increased tumor angiogenesis and cell proliferation, reduced tumor apoptosis. Several studies have reported an inverse relationship between serum TC levels and cancer risk, whereas some found a positive and direct relationship. A prospective Korean cohort study stated that "a high TC level (≥240 mg/dl) was positively related to the prostate, colon cancer in men and breast cancer in women, but negatively associated with risk of liver, stomach cancer in both men and women, and lung cancer in men". Epidemiologic studies suggest that cancer risk is higher for persons who have high serum LDL, cholesterol levels or TG levels. In contrast, another study found an inverse relationship between serum TG and oral cancer.[20] A large population-based cohort study in Sweden indicate that individuals with the total serum cholesterol level of ≥7.0 mmol/L had a 4.5 times higher risk of developing testicular cancer,[21] thus suggesting a relationship between high concentration of cholesterol and risk of testicular cancer. In prospective case–control longitudinal study, the results showed the inverse relationship between serum lipids (TC, TG, HDL cholesterol and very LDL levels) and oral cancer. Furthermore, it has been identified that serum lipid levels did not differ between smokers and nonsmokers groups. As we found in present study, LDL level was lower in BCC patients than healthy ones, which is in line with the results achieved in a Copenhagen population study.[22] In that study, the strong correlation between low LDL cholesterol levels and increased cancer risk was revealed. That study demonstrated that subjects with a LDL cholesterol level lower than 87 mg/dl had a 43% higher risk of developing cancer, compared to persons with higher than 158 mg/dl.[18]

In contrast to our results in the present study, Reddy *et al*.,[23] in a cross-sectional study, analyzed lipid profile in 25 oral cancer patients, compared with control group. Their findings showed a significant increase in LDL, but a decrease in values of HDL, VLDL, TG and TC was observed in the cancer patients group when compared to the controls ($P < 0.05$). Reddy *et al.* suggested that the decrease in lipid profile in cancer patients might be due to their increased utilization of lipids by neoplastic cells in membrane biogenesis. Some studies found a reduced lipid profile in head and neck squamous cell carcinoma patients.[23]

Some researchers have documented the changes in lipid levels in the etiology and prognosis of cancer. In some types of malignancies, such as oral cancers, reduction of cholesterol is alarming for the progression of cancerous lesions.[24]

Given the contradictory results regarding the association between lipid levels and cancer progression, it seems that the pointed association may be potentially influenced by the type of tumor and also by role of lipids in the pathophysiological mechanisms related to cancer progression. As an example, a cross-sectional study showed a significant difference in the lipid profile between different types of cancers (breast, colon, gastric and ovarian). Furthermore, it explained a significant association between higher levels of LDL >110 mg/dl in the serum and metastasis (adjusted odds ratio = 2.4, 95% confidence interval 1.2–3.5), although there was no significant association between lipid profile and lymph nodes involvement and stage of the disease. This study suggested a benefit of measuring serum levels of lipids for predicting cancer progression. Increased LDL levels can be considered a predictive factor for increasing the risk of metastasis. They demonstrated that Lipid profile is not only associated with etiology but also with prognosis in cancer.[24]

They showed a benefit of measuring serum levels of lipids and lipoproteins for predicting different cancer types and their progression. High TG levels were found in patients with ovarian cancer and high levels of cholesterol or HDL in breast cancer patients. Low levels of cholesterol and lipoproteins were reported in gastric cancer patients. Increased LDL levels were significantly associated with metastasis.[24]

Several studies proposed that abnormal lipid profiles may be associated with the occurrence and progression of cancers. Results of some articles indicated that high concentrations of serum HDL are associated with a decreased risk of colon and lung cancer.

This association between HDL-C levels and tumorigenesis can be justified so that, a major function of HDL is to maintain normal cell cholesterol homeostasis by removing excess cholesterol from an intracellular pool. Cancer cells need excess cholesterol and intermediates of the cholesterol biosynthesis pathway to maintain a high level of proliferation is well accepted. The upregulation of cholesterol biosynthesis and uptake are considered to be consistent with carcinogenesis. The possible factors that promote the upregulation of cellular cholesterol synthesis are the abundant availability of precursors (Acetyl-CoA), via glycolysis that potentiates *de novo* fatty acid synthesis. Based on these data, the explanation of the reduction of HDL-C levels in plasma is that the activity of HDL-C receptor pathway was enhanced to prevent the accumulation of intracellular cholesterol during tumor development and lymphatic spread.[11]

Another mechanism includes the involvement of HDL in the regulation of levels of pro-inflammatory cytokines and modulation of oxidative stress. Decreased levels of HDL have been associated with increased circulating levels of pro-inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-*a* receptors, whereas increased levels of HDL-C are related to raised levels of anti-inflammatory cytokines such as IL-10. These pro-inflammatory cytokines are considered to stimulate cellular proliferation and inhibit apoptosis. In addition, HDL protects LDL from oxidative damage, which has been described as a cause of tumorigenesis.[11]

CONCLUSION

In the present study which is the third study about BCC and plasma lipid profiles, determined an increase in levels of all lipid markers examined other than LDL in patients with BCC, and this increase was statistically significant for HDL and Chol. These findings in our study provides evidence that lipids are important in BCC development and support the hypothesis that changes in lipid profile can have an effect on cancer progression. Therefore, changes in plasma levels of lipids can be indicative of the detection of cancerous lesions, although this change may vary depending on different types of cancers and their biological and behavioral characteristics. Hence, there is a need to comprehend the etiology of these skin cancers to identify modifying risks and to expand efficient intervention strategies. Other strategies rather than minimizing UV exposure are needed. Finally, we hope future studies to consider these markers that can significantly affect skin cancer. Finally, iIt seems that changes in lipid profile can help as a diagnostic marker for detecting cancer like BCC. Although this change could be different in lipid markers and also among different types of cancer.

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Conflicts of interest

There are no conflicts of interest.

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