Original Article

Decreased plasma in basal cell cancer

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ABSTRACT

Aim

Basal cell carcinoma (BCC) is one of the most common malignant non-melanoma carcinomas and is an important health problem for all countries. There are many studies on the effect of human lipoprotein metabolism and high-density lipoprotein (HDL-C) function on skin cells, but there are no detailed clinical studies on BCC yet. In addition, higher phospholipid and cholesterol content was found in cancerous and precancerous lesions of the skin compared to normal tissue. The aim of our study was to evaluate the lipid profile in patients with BCC and to try to find any relationship between BCC and molecules that have an important place in HDL-C functionality.

Methods

The patient group consisted of 39 patients who were clinically diagnosed with BCC by biopsy in hospital clinics. The control group (n:44) was randomly selected from patients of the same age group without a diagnosis of BCC who applied to different clinics of the same hospital. Routine lipid level, Apolipoprotein A1 (Apo-A1) level and Paraoxonase (PON-1) enzyme measurements were made from serum samples taken from the patients and control groups participating in the study.

Results

The most important findings of this study, a statistically significant decrease in serum Apo-A1 level and a decrease trend in PON-1 enzyme can be considered in BCC patients compared to control groups.

Conclusion

Lipid metabolism and HDL functionality, may play a role in the development of BCC.

Keywords

Basal cell carcinoma; High-density lipoprotein; Apo-A1; Paraoxonase; Low-density lipoprotein.

INTRODUCTION

Basal cell carcinoma (BCC) is a malignant skin tumor arising from the basal cell layer of the epidermis and its appendages [1, 2]. Although BCC is frequently seen in the elderly population, unfortunately, there has been an increase in the incidence of BCC in young adults in recent years [3]. Unfortunately, BCC is one of the prevailing malignancies in the world today and the incidence of BCC is gradually increasing [4]. Fortunately, the tumor is unlikely to metastasize, but if left untreated, it may grow and cause local invasion and destruction; may result in subcutaneous tissue damage, resulting in loss of function and cosmetic damage. Consequently, early diagnosis and treatment are important [3].

Exposure to solar ultraviolet (UV) radiation is thought to be responsible for the etiopathogenesis of BCC. In addition, age, skin phototype, gender, pharmacological treatment, radiation therapy,

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family history of skin tumors, long-term arsenic exposure, immunosuppression and some genetic syndromes are among the risk factors [1, 5, 6]. Exposure to UV radiation causes wavelength-dependent damage to human skin. UVB directly damages DNA, while UVA's detrimental effects on cellular targets are in the form of photosensitizers and the formation of reactive oxygen species (ROS) [7]. In particular, ROS accumulated intracellularly play a critical role in the intrinsic aging of human skin and photoaging in vivo, therefore it has been suggested that ROS are responsible for various skin cancers and cutaneous inflammatory disorders. Also, oxidative stress induced by UV, apoptotic or necrotic can lead to cell death [8].

In general, cancer cells show specific changes in different aspects of lipid metabolism that can affect lipid signaling functions, including the availability of structural lipids for membrane synthesis, the contribution of lipids to energy homeostasis, and activation of inflammatory pathways. Changes in lipid metabolism are related to important cellular processes, including cell growth, proliferation, differentiation and motility [9]. It has also been reported that alterations in lipid profile and serum lipoproteins are associated with certain skin cancers, comprise BCC. [10, 11]. The multifaceted protective behaviors of high-density lipoprotein (HDL-C) in various physiological and pathological processes and the relationship between cancer biology and lipid metabolism are well known. Thus, there have been numerous studies showing the link between HDL-C function and cancer development and progression.

The relationship between increased oxidative stresses, chronic inflammation, weakened immunity and tumor growth is already well established. In some studies, it has been suggested that HDL-C may also be protective against cancer and the harmful effects of oxidative stress (12, 13). Recent studies show that HDL-C levels and functions are inversely related to cancer risk (14-17). Today, HDL-C mimetics, which are formed from a series of peptides and proteins with various structures, have been used in cancer treatment due to their anti-inflammatory and antioxidant properties similar to HDL-C [18, 19].

Apolipoprotein A1 (Apo-A1) is the major structural protein of HDL-C. Apo-A1 has antioxidant and anti-inflammatory properties as well as antiatherogenic properties. Apo-A1 can inhibit low-density lipoprotein (LDL-C) oxidation, remove lipid hydroperoxides, reduce monocyte chemotaxis, and protect the extracellular matrix from apoptosis [20-22]. In many studies, it has been shown that there is an inverse relationship between the risk of cancer development and HDL-C and Apo-A1 levels [23-25].

One of the important proteins involved in HDL-C structure and function is the Paraoxonase enzyme (PON-1) (26). PON-1 shows peroxidase-like activity and reduces lipid hydroperoxides to hydroxides. It is now known that PON-1 protects against oxidative stress and cancer by hydrolysis of active oxidized phospholipids, destruction of lipid hydroperoxides and H_2O_2, preservation of HDL-C integrity and function, and prevention of LDL-C oxidation [27, 28]. Moreover, a lower activity of serum PON-1 has been reported in cancer patients [28]. Consequently, PON-1 is a lipolactonase that plays a role in the elimination of carcinogenic free radicals and scavenging mechanisms to keep oxidative stability.

Nevertheless, there isn't any study in the literature investigating the relationship between BCC and HDL-C functionality. Thus, in this preliminary study, it was aimed to show the possible relationship between the structural main protein of HDL-C, Apo A1 and the antioxidant PON1 enzyme, with BCC disease.

MATERIALS AND METHODS

Subjects:

Of the patients included in the study, 39 were patients who applied to the Plastic and Reconstructive Surgery Clinic and had lesions/lesions clinically suspected of BCC. The diagnosis of BCC was confirmed by pathological examination of the tissue samples taken from the patients by surgical operation. The control group consisted of 44 individuals (23 males and 21 females) and the patients who applied to different clinics of the hospital were randomly selected among those who did not have a diagnosis or complaint of BCC.

Exclusion criteria of the study; It was determined as using antioxidant drugs, using herbal supplements, using statin-derived drugs and having any of the cancer types other than BCC. Our study is a single-center, in vitro experimental, cross-sectional study. This study was approved by the local ethics committee in accordance with the principles of the 2008 Declaration of Helsinki.

Blood sample:

Blood samples from all participants included in the study were taken into vacuumed yellow capped tubes after 12 hours of night fasting. Then, the blood samples were centrifuged for 10 minutes with a refrigerated centrifuge device, and the serum samples were transferred to eppendorf tubes with plastic caps and stored at -80°C until the time to be analyzed. Hemolyzed and lipemic serum samples were excluded from the study.

Measurements:

Apo-A1 and PON-1 enzyme activity tests were studied from these serum samples obtained and stored from the patient and control groups. In addition, routine lipid measurement (total cholesterol, triglyceride (TG), HDL-C, LDL-C, very low-density lipoprotein (VLDL-C) and non-HDL-C) results were obtained from patient records via the laboratory operating system.

Serum Apo-A1 measurement was performed by quantitative ELISA (Enzyme-Linked Immunosorbent Assay) immunoanalytical method, using Human Apolipoprotein A1 (Apo-A1) ELISA Kit (Catalog No: YLA0883HU, YL Biont®, Shanghai YL Biotech Ltd. China), noncompetitive heterogeneous (sandwich) was performed using the immunoenzymatic measurement technique. BioTek ELx50 (BioTek®, ELX 50, USA) device was used for ELISA test measurement. At the end of the experiment, optical density measurement was made with an ELX 800 BioTek (BioTek®, ELX 800, USA) ELISA reader.

Serum PON-1 activity was measured by reading absorbances with a spectrophotometer (Genesis 10 UV Scanning UV/VIS, Shimadzu) using the Rel Assay® Diagnostics paraxonase assay kit (using spectrophotometric technique).

Statistics:

Statistical analysis of the obtained measurement data was made using MedCalc® Version 19.3 program. Kolmogorov - Smirnov test was used to determine the distribution of the collected data for each variable considered in the study. Un-paired sample t-test was used for countable data with normal distribution, Mann-Whitney U test was used for countable data not normally distributed.

In the comparisons made between the groups formed, as the mean and the distribution range (Minimum - Maximum) at the 95% confidence interval, for the continuous variables conforming to the normal distribution, and as the median and distribution range (Minimum - Maximum) at the 95% confidence interval for the continuous variables not conforming to the normal distribution was expressed. The results of descriptive statistics were used for categorical variables such as gender, known disease, number (frequency) and percentage.

95% confidence level [error (α) = 0.05] was used to determine the differences in the analyses. A probability level of $P < 0.05$ was considered statistically significant.

RESULTS

In the study, there were 21 women (53.8%) and 18 men (46.2%) who had a definitive diagnosis of BCC by 39 biopsies. Also, 44 non-BCC (21 women (47.7%) and 23 men (52.3%)) were in the control group. The mean age of the participants was 70.4 years (95% CI: 67.1 – 71.1) in the patient group and 68 years (95% CI: 64.0 – 70.9) in the control group. Statistically, the age distribution was found in both groups it was normally distributed and no significant difference was found between the mean ages of the two groups (p=0.219).

However, the clinical findings of the patient group include type 2 diabetes (DM) in 11 (28.2%), Hypertension (HT) in 23 (58.9%), cardiovascular disease (CVD) in 7 (17.9%), and 2 (5.1%) had cerebrovascular disease (CVH). In the control group, 14 (31.8%) people had type 2 DM, 17 (38.6%) people had HT, 2 (4.5%) people had CVH, 4 (9.0%) subjects had CVD and 4 (9.0%) subjects had hypothyroidism. Comparison of clinical and demographic data of both groups is shown in Table 1.

Table 1: Demographic characteristics of the patient and control groups

Parameters	Patient	Control
Age (years)	70,4 (%95 CI: 67,1 – 71,1)	68 (%95 CI: 64,0 – 70,9)
Female Gender	21 (%53,8)	21 (%47,7)
Male Gender	18 (%46,2)	23 (%52,3)
DM	11 (%28,2)	14 (%31,8)
HT	23 (%58,9)	17 (%38,6)
CVD	7 (%17,9)	4 (%9,0)
CVO	2 (%5,1)	2 (%4,5)
CRF	0	8 (%18,1)

DM: Diabetes Mellitus, HT: Hypertension, CVD: Cardiovascular disease, CVO: Cerebrovascular disease, CRF: Chronic kidney failure

As a result of the statistical analysis of routine laboratory parameters and serum lipid profile analysis values, no statistically significant difference was found between patient and control group individuals in total cholesterol, TG, HDL-C and VLDL-C values. However, when the serum LDL-C results of the two groups were evaluated, the LDL-C values of the patient group diagnosed with BCC were higher than the control group, and this elevation was found to be statistically significantly different compared to the control group (P=0.003). Similarly, serum non-HDL-C values were higher in the BCC patient group compared to the control group, and there was a statistically significant difference between them. (P=0.006). The serum lipid profile values of the groups are presented in Table 2.

Table 2: Serum routine lipid profile values of the patient and control groups.

Parameters	Patient	Control	p
Total Cholesterol (mg/dL)	**209,2** (%95 CI: 194,5 – 223,9) * (n:34)	**185,5** (%95 CI: 173,7 – 197,3) * (n:44)	0,594
Triglyceride (mg/dL)	**146,2** (%95 CI: 124,0 – 168,3) * (n:33)	**127,2** (%95 CI: 110,0 – 144,4) * (n:44)	0,176
LDL Cholesterol (mg/dL)	**132,5** (%95 CI: 120,3 – 144,7) * (n:32)	**109,9** (%95 CI: 100,8 – 118,9) * (n:44)	**0,003**
HDL Cholesterol (mg/dL)	**50,5** (%95 CI: 45,5 – 55,5) * (n:34)	**50,8** (%95 CI: 46,6 – 55,0)* (n:44)	0,920
VLDL Cholesterol (mg/dL)	**26** (%95 CI: 19,5 – 37,7)** (n:21)	**22** (%95 CI: 19,1 – 27,8)** (n:37)	0,145
Non-HDL Cholesterol (mg/dL)	**158,6** (%95 CI: 144,6 – 172,6) * (n:34)	**134,6** (%95 CI: 124,5 – 144,8) * (n:44)	**0,006**

n: : Number of individuals

* Mean (Distribution range; Minimum-Maximum) / Unpaired t test

** Median (Distribution range; Minimum-Maximum) / Mann-Whitney test

Statistical evaluation of serum Apo-A1 concentration and PON-1 enzyme activity, which are the main parameters of the study, were performed. When the distribution of the obtained data was examined with the Kolmogorov-Smirnov test, it was seen that these variables did not comply with the normal distribution.

As a result, the median values of Apo-A1 concentration were found to be 3063 (95% CI: 2592 – 3552.8) µg/mL and 3640 (95% CI: 3352.4 – 4099) µg/mL in the BCC patient and control groups, respectively. Serum Apo-A1 values were lower in the BCC patient group than in the control group, and there was a statistically significant difference between the groups in terms of Apo-A1 concentrations (P=0.014). The median values of additional PON-1 enzyme activity were 210 (95% CI: 173 – 351.2) U/L in the BCC patient group and 249 (95% CI: 180.4 – 326.2) U/L in the control group. As expected, PON-1 enzyme activity was higher in the control group than in the patient group, and there was no significant difference between the groups, albeit at the limit for statistical significance (P=0.052).The serum Apo-A1 and PON-1 enzyme activity values of the BCC patient group and control group are shown in Table 3.

Table 3: Apo-A1 and PON-1 values of the patient and control groups.

Parameters	Patient (n=39)	Control (n=44)	p
Apo-A1 (µg/mL)	**3063,0** (%95 CI: 2592,0 –3552,8)*	**3640,0** (%95 CI: 3352,4 -4099,0)*	**0,014**
PON-1 (U/L)	**210,0** (%95 CI: 173,0 – 351,2)*	**249,0** (%95 CI: 180,4 – 326,2)*	0,052

n: : Number of individuals

* Median (Distribution range; Minimum-Maximum) / Mann-Whitney test

In addition, the scatter charts of the Apo-A1 and PON-1 enzyme activity concentrations of the patient and control groups are shown in Figure 1, 2.

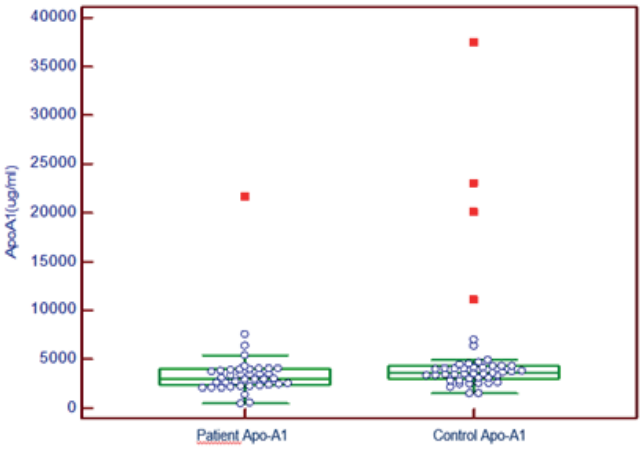

Figure 1: Scatter chart of Apo-A1 levels in the patient and control groups

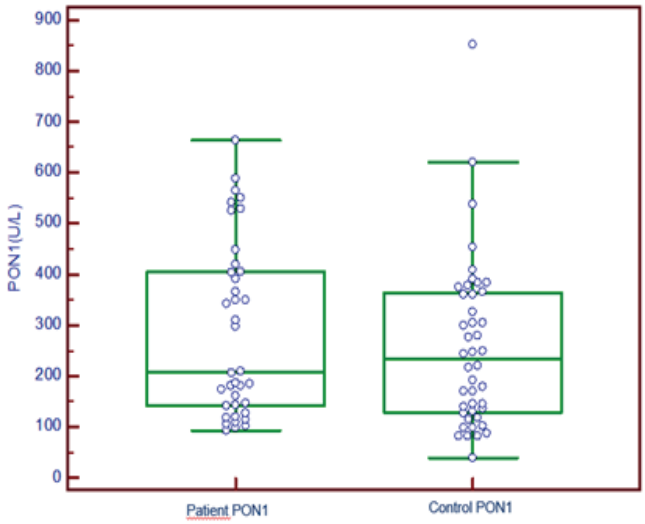

Figure 2: Scatter chart of PON-1 levels in the patient and control groups

DISCUSSION

One of the most important findings of this study is the decreased serum Apo-A1 level in the BCC patient group when the BCC patients are compared with the control group. In addition, although statistically insignificant ($p<0.052$), lower serum PON-1 enzyme activity was detected in the BCC patient group compared to the control group. It is also noteworthy that these two molecules, Apo-A1 and PON1, can also display HDL-C functionality.

These results are a preliminary study for BCC and may be useful for further studies. Because the major structural apolipoprotein of HDL-C, Apo-A1 level is low and the activity of PON-1, one of the most important antioxidant enzymes associated with HDL-C, is lower in BCC patients. It may indicate impaired HDL-C function and decreased antioxidant balance in BCC patients. Therefore, low functional HDL-C and Apo-A1 levels may cause activation of inflammatory processes associated with tumor biology.

There is no study in the literature examining the level of Apo-A1 in BCC patients, but the relationship between different types of cancer and serum Apo-A1 is well known [24, 29, 32, 33]. In humans, cancer can develop as a result of a series of random mutations. Cancer cases are related with genomic events that boost the rate of mutations [30, 31]. Studies have shown that there is an inverse relationship between Apo-A1 levels and the risk of developing breast, colorectal and lung cancer [24, 29]. In addition, Apo-A1 has been found to be specifically and inversely associated with survival in a number of solid tumor types, including esophageal squamous cell carcinoma and renal cell carcinoma, by different researchers [32, 33].

However, the role of ApoA-1 in carcinogenesis is not yet fully understood. It has been stated that Apo-A1 and HDL-C reduce free pro-inflammatory cytokines such as TNF-α, which reduces tissue damage, macrophage and neutrophil infiltration, and reduces the risk of tumor development [34]. Considering the anti-inflammatory, anti-oxidant properties and immune regulatory functions of Apo-A1, it is concluded that this apolipoprotein has a clear potential as an anti-tumorogenic agent. It has been shown that when Apo-A1 is given, the peak tumor and metastasis burden is reduced by 50% within a week [35]. Identifying the potent immune modulatory effects of Apo-A1 with its emerging anti-tumor biological activity, it is conceivable that pharmacological administration of Apo-A1 would provide therapeutic benefit as an anti-cancer agent.

In the tumor microenvironment, it is conceivable that Apo-A1 might work as a potent immunomodulatory agent that converts tumor-associated macrophages from pro-tumor to anti-tumor phenotype [33]. In addition, the anti-tumor activities of Apo-A1 have been shown to correlate with its ability to efflux cholesterol in a mouse model of colorectal cancer and to target mevalonate and serine synthesis pathways in a mouse model of melanoma [36, 37].

The low level of serum Apo-A1 levels in the patient group with BCC, which is among the results of this

study, is consistent with the results of previous studies.

In our study, we observed that HDL-C related antioxidant PON-1 enzyme activity was lower in BCC patients compared to the control group. However, we have seen in the literature that PON-1 enzyme, which is an endogenous free radical scavenger, has not yet been studied in BCC patients. However, the possible role of PON-1 activity in tumor development is well known. In previous studies, low PON-1 activity was found in head and neck cancer patients, oral squamous cell cancer, lung, colorectal and breast cancers [38-40].

In fact, it can be thought that PON-1 may also initiate the carcinogenesis process due to oxidative stress in patients with BCC. For example, in a study conducted in patients with papillary thyroid cancer, PON-1 activity was lower in the patient group and it showed a positive correlation with an antioxidant total free sulfhydryl (-SH) and negatively correlated with oxidant lipid hydroperoxide (LOOH) [41].

Similarly, higher LDL-C and non-HDL-C levels in BCC patients in this study may support the possible role of lipid metabolism disorder in the development of BCC cancer. Lipid metabolism has been recognized as one of the main metabolic pathways related to many aspects of cancer cell development, including signaling processes related to cell transformation and tumor development, and has been supported by numerous studies [42-44].

There are many studies showing that Apo-A1, an important member of blood lipoproteins, plays an important role in the emergence and progression of cardiovascular and oncological diseases. However, no studies have comprehensively evaluated the relationship between the Apo-A1 protein and primary BCC. Apo-A1 belongs to the A1/A4/E apolipoprotein family and has a significant role in lipid metabolism. Therefore, apabetalone, a synthetic stimulant of Apo-A1, can increase both HDL-C and Apo-A1 so that it can be considered an inhibitor against cancer. Phase III studies are ongoing for apabetalone, especially against cardiovascular diseases. Our study results may suggest that therapeutically regulated Apo-A1 may be a new therapeutic target for BCC therapy by modulating lipid metabolism. Further studies on Apo-A1 stimulants such as apabetalone in BCC formation and treatment are warranted [45, 46]. In a study conducted, it can be thought that micronutrients that may have a role in improving weight loss in cancer patients, for example, the use of vitamin D and zinc, may positively affect Apoa 1 levels [47].

CONCLUSION

In conclusion, the main finding of our study is the possible relationship between BCC disease, which is increasingly seen in the population, and Apo-A1. Considering the data of our study, it can be thought that there may be a causal link between the decreased Apo-A1 levels in BCC patients and the progression of the disease. The decrease in serum Apo-A1 level may result in the future use of Apo-A1 peptide mimetics in BCC disease.

In addition, this study draws attention to PON1 enzyme activity, which tends to decrease in BCC patients, and possible lipid metabolism disorders. With these preliminary study findings, it can contribute to the literature in terms of understanding BCC disease and needs to be supported by more comprehensive clinical studies.

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Authors's contribution:

Data gathering and idea owner of this study: COK, NY

Study design: COK, NY

Data gathering: COK, EY

Writing and submitting manuscript: COK, NY, EY

Editing and approval of final draft: COK, NY, EY

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