ISSN: 2717-8161 RESEARCH ARTICLE

New Trend Med Sci 2024; 5(1): 1-6. https://dergipark.org.tr/tr/pub/ntms

Increased Atherogenic Indices and Basal Cell Carcinoma

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Article History
Received 15 May 2023
Accepted 25 Jan 2024
Published Online 30 Jan 2024

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Doi:*10.56766/ntms.1297303*

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Abstract: Atherosclerosis and cancer are chronic diseases that are considered to be two of the most common causes of death. Given that both diseases are chronic multifactorial, they may also share many etiological and mechanistic processes. Inflammatory processes and oxidative stress are also important factors in the development of both atherosclerosis and cancer. The aim of this study is to provide new evidence, not included in the literature, between calculable atherogenicity risk indices and basal cell carcinoma (BCC) formation, and to encourage the identification of closer molecular links between these two pathologies. Atherogenic plasma index (AIP), atherogenic index (AI) and Lipoprotein combined index (LCI) were calculated using mathematical formulas and routine lipid values. The routine lipid parametres and atherogenic index values of the BCC patients (n: 39) were compared with the controls (n: 44). Unpaired t-test were used for parameters with normal distribution and Mann-Whitney test were used for non-normally distributed parameters. Among the serum lipid parameters, only low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) were significantly increased in the patient group. However, all atherogenic indices (AIP, AI and LCI) were found to be statistically significantly higher in the patient group ($p<0.0001$). Atherosclerosis is associated with a variety of comorbidities; this preliminary study showed an increase in atherogenic risk indices in elderly patients with BCC. There is no doubt that index calculations such as AIP, AI and LCI will increasingly be included in cancer research. Future studies with large participation may better show the clinical importance of serum lipid values and atherogenic risk index calculations. ©2024 NTMS.

Keywords: Basal cell carcinoma; Cancer; Atherogenic Index; Lipid.

1. Introduction

Currently, atherosclerosis and cancer are chronic diseases that are accepted as the top two causes of death all over the world. Many factors that play a role in the development of atherosclerosis are also involved in the development and progression of cancer, especially in skin cancers. Genetic changes, inflammatory processes, uncontrolled cell proliferation and increased oxidative stress can be given as examples among the most important risk factors for both atherosclerosis and cancer [1].

Basal cell carcinoma (BCC) is a malignant skin tumor originating from the basal cell layer of the epidermis and its appendages. BCC, which is responsible for 90% of all cutaneous malignancies of the skin, is one of the

Cite this article as: Oz Kaymaz C, Yilmaz N and Eren E. Increased Atherogenic Indices and Basal Cell Carcinoma. New Trend Med Sci. 2024; 5(1):1-6. Doi:10.56766/ntms.1297303.

most common malignancies in the world and its incidence is increasing [2]. Because the skin is the largest body organ that protects it from external factors, which is very important for homeostasis. Many environmental influences such as ultraviolet (UV) from the Sun are oxidant and directly or indirectly catalyze the production of reactive oxygen species (ROS). ROS can damage the skin, largely by directing several key molecular pathways that play important roles in a variety of pathological processes, including atherosclerosis and inflammatory responses. Unfortunately, these cutaneous homeostatic defenses, although highly effective, have limited capacity and can be overloaded and thus lead to increased ROS in the skin, which can promote the development of dermatological diseases [3]. In addition, changes in serum lipid profile and lipoprotein levels have been reported in the pathogenesis of BCC and other skin cancers in previous studies [4, 5]. It may be considered useful to measure atherosclerotic risk indices to predict different types of skin diseases and the progression of these cancers [6-8].

Of course, the main reason why changes in lipid profile have long been associated with cancer is that lipids play a key role in maintaining cell integrity and vascular endothelium. Lipid metabolism has been recognized as one of the major metabolic pathways involved in many aspects of cancer cell developmental function, including signaling processes related to cell transformation and tumor growth [9, 10]. Although serum lipid levels have been investigated in different types of cancer to date, they have revealed conflicting results of the relationship between serum lipid biomarkers and BCC [4, 5]. However, serum proatherogenic lipid profile and atherogenic indices in BCC patients are not yet included in the literature.

Currently, new "atherogenic indices" from various lipoprotein ratios have been defined to optimize the predictive capacity of the lipid profile. These indexes are a simple calculation with no extra cost. Atherogenic plasma index (AIP), atherogenic index (AI) and lipoprotein combined index (LCI) are some of the new indices created [11]. These atherogenic indices are increasingly associated with diseases and are widely used as indicators of dyslipidemia and related diseases [12, 13]. Although they are used as powerful biomarkers to determine the prognostic value of atherogenicity and cardiovascular diseases, they have also been associated with obesity and cancer risk [7, 14].

Studies have shown a correlation between atherogenic indices (AIP, AI) and markers of oxidative stress [15]. It is known that oxidative stress plays an important role in the initiation of carcinogenesis events. The role of atherosclerosis-related oxidative stress in the pathogenesis of many cancers, including BCC, has also been reported by different researchers [15, 16]. Therefore, it is very valuable to investigate the relationship between atherogenic indices and cancers. Since possible lipid metabolism changes in BCC have not been clarified yet, we aimed to examine the relationship between atherogenic indices and BCC in our study.

2. Material and Methods

2.1. Subjects

This study was carried out in a single center at Antalya Training and Research Hospital between September 2019 and February 2021. The patient group included in the study consisted of 39 (18 men and 21 women) patients who applied with a suspicious BCC lesion(s) and were subsequently diagnosed with histopathological BCC. The control group consisted of 44 people (23 men and 21 women) who applied to different clinics of the hospital and were not diagnosed with BCC. All participants of the study were randomly selected in the same process. The number of study subjects was calculated from the prevalence of the disease using the www.Raosoft.com calculator.

People with antioxidant drug use, herbal supplement use, statin-derived drug use, and any of the cancer types other than BCC were excluded from the study. Our study is a retrospective cohort study. This study was approved by the local ethics committee in accordance with the principles of the 2008 Declaration of Helsinki. Written and informed consent forms were obtained from the participants.

2.2. Methods

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 obtained. TC analysis by cholesterol oxidase enzymatic method (Beckman® coulter total cholesterol kit), TG analysis by Glycerophosphate Oxidase enzymatic method (Beckman® coulter triglyceride kit), HDL-C analysis by Cholesterol Oxidase enzymatic method (Beckman® coulter HDL cholesterol kit) were measured in autoanalyzer. LDL-C results were calculated using the Friedewald formula, as fasting serum TG values of all participants were <400 mg/dl. Also, VLDL results were obtained by calculating (VLDL=TG/5). Thereafter each patient's atherogenic indices were calculated from mathematical formulations and various lipoprotein ratios.

For example, AIP was first calculated as the logarithmic transformation of the ratio of TG level to HDL-C level. AIP = log10 (TG/HDL-C)

AI is defined as the ratio of non-HDL-C to HDL-C and is calculated using the formula: AI=non-HDL-C/HDL-C (non-HDL-C=TC - HDL-C).

LCI is calculated using the formula: LCI= (TC x TG x LDL)/HDL-C.

2.3. Statistical Analysis

Statistical analysis of the calculated lipid index data was performed 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.
Unpaired sample t-test was used for countable data with normal distribution, and Mann-Whitney U test was used for countable data without normal distribution.
In the comparisons made between the groups created, descriptive statistics showing for the continuous variables with normal distribution at the 95% confidence interval, the mean and standard deviation (SD); for the continuous variables that do not fit the normal distribution at the 95% confidence interval, the median and interquantile range (IQR) has been done. Descriptive statistics results were used for categorical variables such as gender, known disease, number (frequency) and percentage.
A 95% confidence level [error (α)=0.05] was used to identify differences in analyzes. A probability level of P<0.05 was considered statistically significant.

3. Results

There were 39 patients in the study, 21 women (53.8%) and 18 men (46.2%), who were diagnosed with definitive BCC by biopsy. 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 71±10.6 years in the patient group and 68±7.5 years in the control group. Statistically, the age distribution was found normally distributed in both groups 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 cerebrovascular disease (CVd) in 2 (5.1%). In the control group, 14 (31.8%) people had type 2 DM, 17 (38.6%) people had HT, 2 (4.5%) people had CVd, 4 (9.0%) subjects had CVD. 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)	71±10.6 *	68±7.5 *
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)
CVd	2 (5.1%)	2 (4. %5)

DM: Type 2 diabetes, HT: Hypertension, CVD: Cardiovascular disease, CVd: Cerebrovascular disease. * Mean ± SD / Unpaired t test.

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±42.15 * (n:34)	185.5±38.71 * (n:44)	0.594
Triglyceride (mg/dL)	146.2±62.5 * (n:33)	127.2±56.5 * (n:44)	0.176
LDL Cholesterol (mg/dL)	132.5±33.86 * (n:32)	109.9±29.78 * (n:44)	0.003
HDL Cholesterol (mg/dL)	50.5±14.3 * (n:34)	50.8±13.85 * (n:44)	0.920
VLDL Cholesterol (mg/dL)	26 (19.0-40.75) ** (n:21)	22 (17.5-29.0) ** (n:37)	0.145
Non-HDL Cholesterol (mg/dL)	158.6±40.17 * (n:34)	134.6±33.37 * (n:44)	0.006

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol. n: Number of individuals, * Mean±SD/Unpaired t test, ** Median (IQR: Interquantile Range)/Mann-Whitney U test.

In our study, atherogenic plasma indices were calculated over routine serum lipid concentrations. AIP, AI and LPCI values of the patient and control groups were compared statistically. The median AIP value in the patient group was 1.02 (IQR: 1.01-1.03) and 0.31 (IQR: 0.30-0.33) in the control group. The median AI values were 3.13 (IQR: 3.12-3.14) in the patient group and 2.65 (IQR: 2.64-2.65) in the control group. The median LPCI values were 23.3 (IQR: 23.22-23.23) in the patient group and 14.67 (IQR: 14.65-14.67) in the control group. When the median values of AIP, AI and LPCI were compared between the groups, respectively, a statistically significant difference was observed in all three values (P<0.001) (Table 3).

Table 3: Atherogenic plasma indices of patient and control group.

Parameters	Patient	Control	p
AIP**	1.02 (1.01-1.03)* (n=15)	0.31 (0.30-0.33)* (n=16)	<0.001
AI	3.13 (3.12-3.14)* (n=15)	2.65 (2.64-2.65)* (n=18)	<0.001
LCI	23.23 (23.22-23.23)* (n=16)	14.66 (14.65-14.67)* (n=16)	<0.001

AIP: Atherogenic plasma index, AI: atherogenic index, LCI: lipoprotein combined index n: Number of individuals. *Median (IQR: Interquantile Range)/Mann-Whitney U test, **It has been suggested that AIP values between -0.3 and 0.1 are associated with low risk, 0.1 and 0.24 are associated with moderate risk, and values above 0.24 are associated with high atherogenic risk.

4. Discussion

One of the most important findings of our study is that API, AI and LCI values, which are atherogenic index markers, were all found to be significantly higher in the BCC patients when the BCC patients group were compared with the control group. In addition, the higher LDL-C and non-HDL-C levels in BCC patients support the possible role of lipid metabolism in the development of cancer. Although there was no significant difference in routinely measured total cholesterol, TG and HDL-C levels in our study between BCC patients and control group individuals, the fact that atherogenic indices were significantly higher in cancer patients suggests that atherogenicity and atherogenic indices may play a role in BCC disease. It can be expected that the results of the study, which have not yet been adequately covered in the literature, will be preliminary and make a significant contribution to the literature.

Because many studies have been conducted that show that lipids and lipoproteins may be associated with the risk of developing cancer in various types of cancer, and it has been reported that there is a direct relationship for some lipids [17]. Meanwhile, the relationship between lipid biomarkers in serum and plasma and BCC has conflicting results, suggesting that the mechanism of lipid metabolism in BCC is still unclear and requires further investigation. In one of the studies on this subject, the lipid profile of BCC patients and healthy adults was compared; however, no significant difference was observed between the groups in cholesterol, TG, LDL-C and HDL-C levels [5]. In a recent study, an increase was found in the levels of all lipid markers (TG, cholesterol, HDL-C) except LDL-C in patients with BCC, and this increase was statistically significant for HDL-C and cholesterol values [4].

Lipid metabolism has been recognized as one of the major metabolic pathways in cancer cell developmental. Related to this, it was investigated whether exposure to systemic environment enriched with LDL-C promotes breast cancer progression. As a result of the study, it was observed that exposure to LDL-C in breast cancer cell lines induces cell proliferation, migration, and loss of adhesion, which are hallmarks of the epithelial-to-mesenchymal transition process [18]. In another study conducted in patients with breast and prostate cancer, although a significant relationship could not be shown between increased cancer risk and LDL-C, LDL-C/HDL-C ratio was found to be associated with an increased risk of general cancer [19].

Non-HDL-C represents the portion of blood cholesterol that is not considered good cholesterol. Calculation of the non-HDL-C concentration allows to measure the total amount of proatherogenic lipoproteins containing Apolipoprotein B [20]. Non-HDL-C is a more comprehensive measure of atherogenic particles than LDL-C, and non-HDL-C may be superior to LDL-C in its ability to predict cardiovascular events. There are studies investigating the role of non-HDL-C in cancer as well as cardiovascular events. In a study parallel to the results of our study, the lipid profile of women with benign and malignant breast cancer was evaluated and a positive correlation was shown between non-HDL-C levels and breast cancer patients [21]. In studies conducted in patients with lung and endometrial cancer, no significant relationship was found between non-HDL-C and cancer risk [22, 23].

Atherogenic indices and lipid ratios, which are new to the literature and are being used frequently, gain importance especially in the evaluation of CVD risk. These indices have been a strong indicator of the risk of atherogenicity by expressing the imbalance between atherogenic and anti-atherogenic lipoproteins, which routine lipid parameters cannot show [24]. AIP was defined as a predictive marker for plasma atherogenicity and it was stated that it showed the risk of atherosclerosis according to the values obtained. It has been suggested that AIP values between -0.3 and 0.1 are associated with low risk, 0.1 and 0.24 are associated with moderate risk, and values above 0.24 are associated with high atherogenic risk [25]. Accordingly, a large study has shown that there is a significant relationship between AIP and CVD risk factors. In addition, there was a significant positive correlation between AIP and total cholesterol, LDL-C and TG, while a significant negative correlation was observed between AIP and HDL-C [24]. In our study, while the mean AIP values of the patients with BCC were at high risk, the mean AIP values of the control group were found to be lower.

We have not yet come across a study evaluating new atherogenic indices in BCC patients in the literature. However, there are studies showing the relationship of new atherogenic indices with cancer risk in different cancer types. For example, in a study conducted in breast cancer patients, high AIP levels were observed in cancer patients [7]. In a study evaluating lipid derivatives for postoperative gastric cancer mortality, it was shown that preoperative lipid derivatives, especially AI and LDL-C/HDL-C ratio, were strong

predictors of gastric cancer mortality [26]. Different investigators have also conducted studies evaluating AIP to predict malignant renal masses in the preoperative period. In a study, the AIP value of malignant cases was found to be significantly higher than benign cases. In conclusion, it has been stated that AIP can be used as a predictive tool in the suspicion of malignant renal mass [27].

The role of oxidative stress in the pathogenesis of human skin cancers, including BCC, has been reported by many researchers [28, 29]. It has been suggested that the decrease in plasma antioxidant levels in patients with BCC is due to prolonged exposure to UV radiation [29]. The relationship between atherogenic indices AIP and AI and oxidative stress markers has been examined in different studies and a positive correlation has been shown between [15]. The fact that atherogenic indices were found to be significantly higher in cancer patients in our study suggests that atherogenicity and indices showing it may play a role in BCC disease.

One of the limitations of our study is the limited number of participants included in the groups. In addition, since BCC is a type of cancer that occurs at an advanced age, the average age of the control group was kept high. It is inevitable that both the patient group and the control group have comorbid diseases related to advanced age. Not surprisingly, these diseases are associated with atherogenicity, which may have been reflected in the results of the study.

5. Conclusions

The main finding of this study is the high atherogenic indices in BCC disease, which is increasingly seen in the community. Considering the relationship between atherogenicity and BCC, it should be considered that atherogenic indices can be used as an additional tool for predicting malignancy in BCC disease, since it is easy and inexpensive to calculate.

Of course, the findings of our study are preliminary and need to be supported by larger-scale clinical studies.

Limitations of the Study

The limitations of the study are small sample size, retrospective design and potential population bias (represents only patients in our institution). Also, homogenization could not be achieved in terms of other parameters that will affect the indexes.

Acknowledgement

This study received no financial support from anywhere. Thanks to the entire research team for their scientific contributions and insights in the preparation of the study with the principles of high ethics, honesty and openness.

Conflict of Interests

The authors declare no conflict of interest.

Financial Support

This study received no external funding.

Author Contributions

Conceived and designed the experiments; COK, NY, EY. Analyzed and interpreted the data; COK, NY, EY. Contributed reagents, materials, analysis tools or data; COK, NY, EY. Wrote the paper; COK, NY, EY. Study of biostatistics; NY.

Ethical Approval

Ethics committee approval no. 2021/18 was received for this study from the SBU Antalya Training and Research Hospital Clinical Research Ethics Committee.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

The patient and control group who agreed to participate in the study signed the informed consent form.

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