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Correlation of leptin and adiponectin receptor expression with clinicopathological parameters in colorectal carcinoma – A cross-sectional prospective study

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HIGHLIGHTS

- Radical CRC specimens were subjected for histopathological examination. Immunohistochemistry (IHC) was done for the leptin and adiponectin receptors on paraffin embedded tissue sections. The tissue IHC expression was analyzed and was correlated with various clinicopathological parameters.
- The results concluded that positive expression of leptin was associated with lymph node spread and advanced stage of CRC. Negative expression of adiponectin was associated with metastatic spread of CRC.

ABSTRACT – **Background –** Colorectal carcinoma (CRC) is one of the common carcinomas with a rising incidence of metastasis due to its advanced stage of presentation. The existing biomarkers such as CEA (Carcinoembryonic antigen) etc., for prognosis, have low sensitivity and specificity. Hence a need for a newer definitive biomarker. Obesity is the leading cause of CRC. Leptin and adiponectin secreted by adipose tissue have been studied as potential biomarkers in the field of CRC. The present study helps to understand the association of leptin and adiponectin receptors with clinicopathological parameters. **Objective –** To correlate the various clinicopathological parameters with the tissue expression of leptin and adiponectin receptors in CRC. **Methods** – It is a cross-sectional prospective study conducted at a tertiary care hospital. Formalin fixed paraffin blocks of all radical resection CRC cases were collected and immunohistochemistry (IHC)was carried out on tumor tissue for leptin and adiponectin receptor. Tumor characteristics and clinical parameters were collected from the hospital medical records. Pearson's correlation coefficient test was used. **Results –** Immunohistochemistry was performed on 60 cases of CRC. Significant positive correlation of leptin was observed with size, lymph node metastasis, advanced stage, and grade of tumor (P<0.05). A significant correlation between adiponectin receptor and CRC was observed concerning age, stage, lymph node metastasis, distant metastasis and grade of tumor. **Conclusion –** Positive expression of leptin and negative expression of adiponectin receptors in CRC helps to predict the risk of metastasis.

Keywords – Colorectal carcinoma; leptin; adiponectin receptor; immunohistochemistry.

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INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common cancers in India[1]. Recent figures have shown an increasing trend in the incidence rate (5.8 in 2004 to 6.9 per 100.000 habitants in 2014) and mortality rate[1]. Obesity, low fiber diet, and familial syndromes are etiological factors for CRC. Obesity is one of the leading global health problems and a serious concern in countries like India due to habits such as calorie-rich diets, sedentary lifestyles, and increase screen time (watching television, computer, and mobiles[2]. Cancer incidence progresses with an increase in BMI[2].

BMI, body fat and waist circumference are speculated to be associated with cardiovascular disease, diabetes, and cancers including CRC[3]. In the current scenario, clinicopathological parameters are valued to be very important in treatment modalities for CRC. Only a few biomarkers with low sensitivity exist and hence there is a need for a definitive (highly sensitive/specific) biomarker for colorectal carcinoma. Adipose tissue of the body is an endocrine organ that secretes adipokines like leptins and adiponectin[4]. Leptin is a 16K Da, non-glycosylated protein, derived from adipocytes[5]. The receptor has 5 isoforms (Ob-R) and belongs to cytokine class 1 family receptors. They are Ob-Ra, Rb, Rc, Rd, and Rf[5]. Leptin acts via Ob-Rb via JNK, mTOR, and AKT pathways, thereby promoting tumorigenesis[6]. Adiponectin is a 30kDa protein with 247 amino acids polypeptide coded by adipoQ cDNA in adipose tissue[7,8]. Adiponectin levels are usually measured in serum and not expressed on the epithelial cells. AdipoR1, AdipoR2 and T-Cadherin receptors are the three receptors for adiponectin protein[8]. It acts through the AMPK pathway and promotes anti-inflammatory and anti-tumorigenesis[9]. Hence both are inversely associated with cancer[4]. Previous studies show that the levels of leptins increase whereas adiponectin levels decrease with obesity and carcinomas[10,11]. Moreover, related data from the Indian population is very scarce. The aim of the study is to identify the frequency of leptin and adiponectin receptor expression in colorectal cancer and to correlate the various clinicopathological parameters with the tissue expression of leptin and adiponectin receptors in CRC.

METHODS

In this cross-sectional study design, all the samples were collected from tertiary care hospitals. All the samples were collected from tertiary care hospitals after obtaining institutional Ethical Committee Approval (IEC Number-SDMCDS IEC. No. 2021/Medical/Ph.D./Pathology/01). Paraffin-embedded blocks of all radical resection of CRC were collected from the department of pathology at a tertiary care hospital for IHC studies (leptin, adiponectin receptor). Clinical data and tumor characteristics such as gender, age, BMI were collected from hospital records and also from clinical history of patients. Tumor size, histological type, stage, grade, tumor extension and lymph node involvement were assessed by histopathological examination. Metastatic CRC were identified based on radiology reports. All formalin fixed paraffin blocks of radical colectomy specimens diagnosed with colorectal carcinoma were included in the study. Colorectal carcinoma cases associated with familial adenomatous polyposis, colorectal adenocarcinoma with inflammatory bowel disease, radiation colitis, colonic adenomas and malignancy of organs other than colon were excluded from the study.

Sample size estimation was done based on the serum leptin levels in colorectal carcinoma using G. Power sample size estimation software (version 3.1.9.2) and previous study by Erkasap N, 2013[12]. A minimum of 60 cases were calculated for the study. Histopathological examination was performed and all colorectal carcinomas were diagnosed according to WHO classification (5th edition, 2019)[13] and staging was done according to TNM staging (American joint cancer committee 8th edition)[14]. Early-stage CRC includes stage 0, I, II and advanced stage CRC includes stage III, IV.

4 µm thick sections were taken on positively charged slides. After overnight incubation at 37ºC and deparaffinization with repeated washes of xylene (10 mins each) followed by rehydration of tissues with graded alcohol was done. The slides were then washed with running water (10 mins) and distilled water (5 mins) following which antigen retrieval with citrate or EDTA buffer at 95ºC was done and cooled at room temperature. Peroxide block was carried out for 10–15 mins and washed in phosphate buffer so-

lution (PBS) for 5 mins and incubated with primary antibody (Primary antibodies are anti-leptin rabbit polyclonal antibody and polyclonal anti-adiponectin receptor antibody ADIPOR1 &ADIPOR2) in 1: 250 dilutions with reagent – antibody diluents as per manufacturer's instructions (Wuhan Fine Biotech Co. Ltd, Wuhan, China) for 45 min. Subsequently, tissues were incubated with poly excel target binder for 15 to 20 mins and washed with PBS for 5 mins. Incubation was again done with HRP for 15 to 20 mins, washed with PBS for 5 mins, and developed with DAB (Diaminobenzidine) chromogen for 5–8 mins. Every staining run contained a slide treated with tris buffer in place of the leptin antibody as a negative control. Sections of benign breast lesion with ductal epithelial cells displaying cytoplasmic positivity was used as positive controls for leptin and adiponectin receptors.

Immunoreactivity score (IRS) classification scoring systems[15] were used for leptin and adiponectin receptor as shown in TABLE 1.

For statistical purposes, the results of IRS scores were divided as follows:

Negative, mild staining=negative expression of leptin and adiponectin receptor.

Moderate, strong staining=positive expression of leptin and adiponectin receptor.

Statistical analysis

Descriptive statistics like demographic details and clinicopathological details are expressed as a percentage, mean and range. Leptin and adiponectin receptor expression was expressed in percentages. Descriptive statistical analysis was carried out to present the characteristics of the patients and IHC expression levels of proteins. Correlation between the histopathological grading, stage, BMI, IHC expression values of leptin and adiponectin receptor was done using Pearman's correlation coefficient using software PRISM 7 for Windows version 7.04, November 2017. A *P*-value of less than 0.05 was considered to be statistically significant for all comparisons.

RESULTS

A total of 60 cases were studied. Correlation of the demographic, clinical, radiological, biochemical, histopathological findings with IHC values of leptin and adiponectin receptor are illustrated in TABLE 2. IHC results of leptin and adiponectin receptors are shown in TABLE 3. Out of 60 cases studied, 32 cases were of early stage (pathological stage 0, I, II) and 28 cases (pathological stage III, IV) were of advanced stage.

Positive expression of leptin was seen in 78% of the cases.

Positive expression of leptin was observed in CRC when compared to non-cancerous colonic tissues. A positive association of leptin expression was observed with size, advanced stage and lymph node metastasis. A negative association of leptin expression was observed with the grade of the tumor. Decreasing gradient of leptin expression was observed from grade 3 to grade 1 (FIGURE 1).

Comparison of leptin expression was also significant with respect to early stage and advanced stage CRC (GRAPH 1) ($P<0.05$).

No significant association of leptin IHC expression in CRC cases concerning age, gender, BMI, tumor site, histological type, tumor extension, lymphovascular invasion, distant metastasis was observed.

Positive expression of adiponectin receptor was seen in 65% of the cases. A positive correlation between adiponectin receptor and CRC was observed for age and distant metastasis. Expression of adiponectin receptor was also significant with respect to early stage and advanced stage CRC (GRAPH 2) ($P<0.05$). Decreasing gradient of adiponectin receptor expression was observed from grade 3 to grade 1 (FIGURE 2).

TABLE 1. IRS scoring system[15] for leptin and adiponectin receptor expression.

Percentage of positive cells x Intensity of Staining			IRS classification
0 = no positive cells	0 = no reaction	0–1 = negative	0 = negative
1=<10% of positive cells	1 = mild reaction	2–3 = mild	1 = positive, weak expression
2=10–50% positive cells	2 = moderate reaction	4–8= moderate	2 = positive, mild expression
3=51–80% positive cells	3 = strong reaction	9–12= strongly positive	3 = positive, strong expression
4=>80% positive cells			

IRS: Immunoreactivity score.

TABLE 2. Correlation of Histopathological features with leptin and adiponectin receptor expression.

Parameters		Number of cases and percentage	Leptin			Adiponectin receptor		
			Negative	Positive	*P*-value	Negative	Positive	*P*-value
Age	<50 years	21 (35.5%)	11 (52.3%)	9 (42.8%)	Not significant	16 (76.1%)	05 (23.8%)	**Significant *P*<0.05**
	>50 years	39 (64.5%)	30 (76.9%)	9 (23.07%)		23 (58.3%)	16 (41.02%)	
BMI	>25 Overweight	18 (30%)	11 (61.1%)	7 (38.1%)	Not significant	13 (72.2%)	5 (27.7%)	Not significant
	<25 Normal	42 (70%)	30 (71.4%)	12 (28.5%)		28 (66.6%)	14 (33.3%)	
Grade	Well	46 (76.6%)	31 (67.4%)	15 (32.6%)	**Significant *P*<0.05**	29 (63%)	17 (37%)	**Significant *P*<0.05**
	Moderate	9 (15%)	7 (77.8%)	2 (22.2%)		7 (77.8%)	2 (22.2%)	
	Poor	5 (8.3%)	2 (40%)	3 (60%)		4 (80%)	1 (20%)	
Tumor extension	In situ	1 (1.6%)	0	1 (100%)	Not significant	1 (100)	0 (0)	Not Significant
	T1	3 (5%)	2 (66%)	1 (25%)		1 (33%)	2 (66.7%)	
	T2	11 (18.35%)	8 (72%)	3 (30%)		9 (81%)	2 (18.2%)	
	T3	37 (61.6%)	24 (64.9%)	13 (35%)		22 (59.5%)	15 (45%)	
	T4	8 (13.35%)	6 (75%)	2 (25%)		7 (87.5%)	11 (12.5%)	
Lymph Node deposits	Positive	19 (46.3%)	16 (66.7%)	8 (33.3%)	**Significant *P*<0.05**	13 (54.2%)	11 (45.8%)	**Significant *P*<0.05**
	Negative	22 (53.7%)	24 (66.7%)	12 (33.3%)		27 (75.0%)	9 (25%)	
Distant metastasis	Mx	30 (73.2%)	30 (71.4%)	12 (28.6%)	Not Significant	26 (61.9%)	16 (38.1%)	**Significant *P*<0.05**
	M0	8 (19.5%)	9 (64.3%)	5 (35.7%)		11 (78.1%)	3 (21.4%)	
	M1	3 (7.3%)	1 (25.%)	3 (75%)		3 (75%)	1 (25%)	
TNM stage	0	1 (2.4%)	0	2 (100%)	**Significant *P*<0.05**	1 (50%)	1 (50%)	**Significant *P*<0.05**
	I	4 (9.8%)	0	4 (36%)		8 (72.7%)	3 (27.3%)	
	II	16 (39%)	5 (55.6%)	4 (21%)		13 (68.4%)	6 (31.6%)	
	III	17 (41.5%)	4 (44.4%)	7 (30%)		14 (60.9%)	09 (39.1%)	
	IV	3(7.3%)	0	3 (60.1%)		4 (80.9%)	1 (20%)	

TABLE 3. Leptin and Adiponectin receptor expression in colorectal carcinoma:

	Leptin	Adiponectin receptor
Negative expression	40 (66.6%)	40 (66.6%)
Positive expression	20 (33.3%)	20 (33.3%)

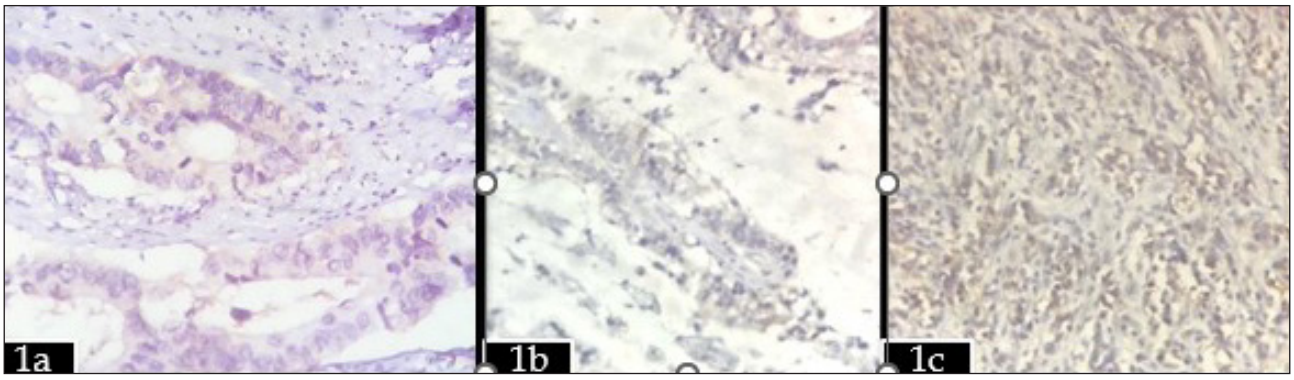
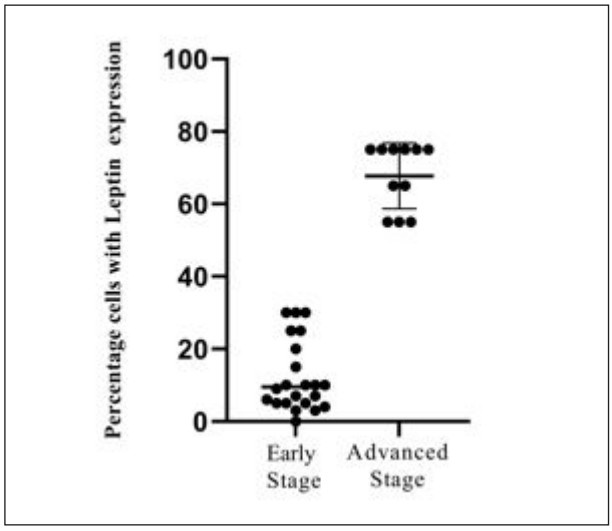
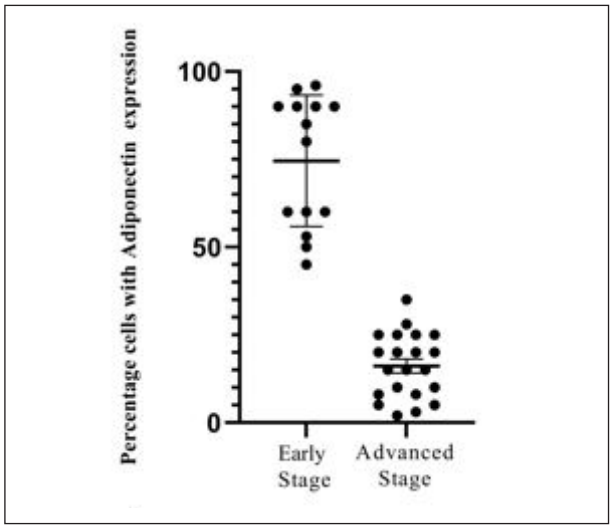


FIGURE 1. Decreasing gradient of leptin expression observed from grade 3 to grade 1.
1a -grade 1 CRC, 1b -grade 2 CRC, 1c - grade 3 CRC.
CRC: colorectal carcinoma.



GRAPH 1. Depicting significant difference in the expression of leptin between early stage CRC and advance stage CRC (P<0.05).
CRC: colorectal carcinoma.



GRAPH 2. Depicting significant difference in the expression of adiponectin between early stage CRC and advance stage CRC (P<0.05).
CRC: colorectal carcinoma.

A negative association of adiponectin receptor for CRC was observed for the grade of the tumor, stage of the tumor and lymph node metastasis.

No significant association of adiponectin receptor expression was observed in CRC for gender, BMI, tumor site, histological type, tumor extension, tumor size, lymph vascular invasion.

DISCUSSION

The Leptin gene Ob is present on chromosome number 7[5]. The receptor has 5 isoforms (Ob-R) and belongs to cytokine class 1 family receptors. Ob-Rb is the leptin receptor that has been vastly studied[5]. Physiologically Leptin plays a significant role as an energy balancer by acting on the hypothalamus through POMC /CART and NPY / AgRP neurons[16]. It acts in immune modulation, and tissue repair, induces monocyte chemoattractant protein, and activates hematopoietic cells[16,17].

Adiponectin belongs to the Tumor necrosis factor (TNF) family[7,8]. Physiologically, Adiponectin acts through the AMPK pathway and helps in follicular growth, fetal development, and embryo implantation, and maintains insulin sensitivity[9]. Adiponectin acts as an anti-inflammatory protein and inactivates IL-6, IL-10, TNF alfa, and IFN gamma. Adiponectin plays an important role in carcinoma prevention by inhibiting angiogenesis and cell proliferation[9].

Leptin and adiponectin are the two adipokines that are deregulated in obesity and obesity-related carcinoma[18]. Koda et al. showed a significant positive association between IHC expression of leptin and tumor grade and stage whereas Paik et al. showed

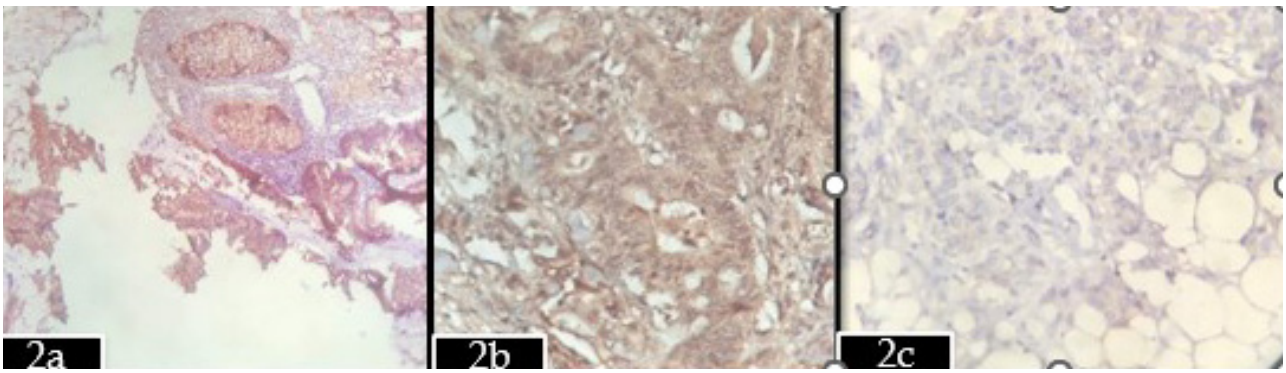


FIGURE 2. Decreasing gradient of adiponectin receptor expression observed from grade 3 to grade 1.
2a -grade 1 CRC, 2b -grade 2 CRC, 2c - grade 3 CRC.
CRC: colorectal carcinoma.

an inverse relation on stage and grade of tumor[19,20]. Inconsistency persists in leptin expression among normal colonic mucosa, colonic adenoma, and colorectal carcinoma[19] Many studies have been performed on serum leptin and are independent of BMI[21]. A study done by dos Santos et al. for adiponectin showed that adiponectin downregulated the leptin pathway in breast cancer cell lines[18,22]. Due to varied and inconclusive findings in different literature, the present study is done on clinical CRC samples to find the association of leptin and adiponectin receptors in CRC cases.

Leptin expression and colorectal carcinoma

Positive expression of leptin was seen in 78% of the cases. Positive association was found in CRC with size >5 cms, advanced stage and lymph node metastasis. However, negative expression of leptin protein was observed with a higher grade of tumor.

Positive expression of leptin is associated with increasing size (>5 cms) of the tumor similar to the findings in other studies. This finding supports the fact that leptin helps in the growth and replication of tumor cells[6]. In the present study, lymph node metastasis was associated with positive expression of leptin similar to the finding by Lui et al. in CRC[23].

A positive association was seen with the increase in the stage of the tumor similar to the finding by Lui et al.[23]. This supports the fact that leptin is involved in the progression of the tumour. Studies have shown that binding of leptin to its receptors cause synergism between leptin and VEGF[24], thereby promoting angiogenesis, invasion and metastasis[12].

Negative expression of leptin protein was observed with a higher grade of tumor similar to the findings by Paik et al.[20]. The probable reasons are: 1) Leptin is degraded in high grade tumors due to the activation of other factors like VEGF, E -Cadherin, and MMPs. Hence there is a negative leptin expression in high-grade tumors[12]. 2) High grade tumors also show silencing of leptin gene[19] 3) Leptin mRNA expression is induced by hypoxia. Leptin gene promoter is regulated by hypoxia-inducible factor (HIF-1alfa). HIF-1alfa is decreased in high--grade tumors, thereby reducing the expression of the leptin gene[12].

Our study showed that there was no correlation between leptin and BMI. This is contrary to other studies which showed a strong association of high BMI with the development of cancer due to high leptin levels[27]. However, our study did not find an association between BMI and CRC at the time of presentation. Most of the cases were in stage 3 and advanced tumor extension (T3). The cause of normal/low BMI could be due to cancer cachexia in the advanced stage, at the time of presentation according to the present study.

Our study demonstrates increasing positive expression of leptin from adjacent mucosa to carcinomatous tissue, similar to the findings by Paik et al.[20]. However, inconsistency persists in leptin expression among normal colonic mucosa, colonic adenoma and colorectal carcinoma among studies. Koda et al. showed low leptin levels in normal than adenoma and adenocarcinoma[19].

Adiponectin receptor expression and colorectal carcinoma

Positive expression of adiponectin receptor was seen in 65% of the cases. Positive expression of adiponectin receptor and CRC was observed for older age, distant metastasis. Negative expression of adiponectin receptors for CRC were observed for tumor grade, advanced stage and lymph node metastasis.

Positive expression of adiponectin receptor was found in patients with older age. Studies have shown that adiponectin levels are low in older patients either due to there is loss of function of circulation adiponectin or the destruction of adiponectin molecules due to increased inflammatory processes in aged individuals[25]. This suggests that the tumor protective levels of serum adiponectin diminish as age progresses. Lower circulating adiponectin in CRC causes a compensatory response in the malignant cells to produce more and more receptors. It is also a general pharmacological fact that whenever the first messenger is decreased then its receptor is increased (upregulation-downregulation). Hence, we have positive expression of adiponectin receptors in older age groups.

Negative expression of adiponectin receptor was found in an advanced stage of the tumors. Michalakis et al. studied ADIPOR1 in prostate carci-

noma and showed an inverse association between adiponectin and the stage of tumor[26]. Yoneda et al. studied IHC and mRNA expression status of adiponectin receptors on normal and CRC[27]. But there was no significant difference in the receptor expression between normal and CRC tissues. He also described that adiponectin receptors were higher in advanced CRC[27].

Adiponectin receptor decreased expression was found in higher-grade of tumors. This study also hypothesizes that decreased adiponectin receptors in high grade tumors may be likely due to the association of adiponectin receptors with the cell adhesion molecules. Cell adhesion molecules are lost in high-grade tumors, thereby loss of adiponectin receptors.

Our study observed that adiponectin receptors are negatively expressed in cases with lymph node metastasis which is similar to the study done by Hiyoshi M et al.[28]. This can be due to the escape mechanism by the tumor cells against the protective effect of the adiponectin[28]. There is no association between BMI and adiponectin receptor expression in the present study. Jeong et al. found that there was no association between BMI and adipokines[21].

Leptin and adiponectin receptors are associated with CRC irrespective of BMI status. Ethnicity and dietary habits play a more vital role in the development of CRC than any other cancer suggested by Otake et al.[29]. Since Indian ethnicity, lifestyle, and habits significantly differ from the rest of the world, it is important to know about the effect of these adipokines in the Indian population. The present study helps to develop a screening tool for colorectal carcinoma prevention. The study will support many other studies which will focus on the development of targeted therapy against leptins in colorectal carcinoma. Based on the association of the adiponectin receptor with clinicopathological parameters, the study proposes that the leptin and adiponectin receptor can be utilised like estrogen receptor and progesterone receptor in breast carcinoma for prognostication, and molecular classification in CRC. It can also be used on endoscopic biopsies of the CRC for prognosis and pre- operative therapy and management.

Limitation: Equal distribution of cases was not possible in stage I, II, III, IV CRC in the study. mRNA studies for adipokines and follow up studies are recommended to know the actual relation with CRC.

To the best of our knowledge, this study is the first of its kind to evaluate the correlation between the IHC of the leptin protein and adiponectin receptors in early stage and advanced stage colorectal carcinoma cases in the Indian population. Several studies have performed leptin serum level expression in CRC cases. However, leptin in the serum is influenced by major factors like inflammation, diabetes, hypertension, aging, etc. The tissue expression status of these proteins is more promising than serum estimation.

CONCLUSION

Leptin and adiponectin receptor immunostaining are a useful method in predicting cases with risk of the advanced stage of CRC/progression of carcinoma. Positive expression of leptin is associated with high risk of metastatic CRC. Negative expression of adiponectin receptor in CRC leads to loss of protective role of adiponectin, leading to spread of CRC.

Authors contribution

Parmesh P: conceptualization, study design, definition of the intellectual contents, literature search, data acquisition and analysis, manuscript preparation and editing. Dinesh US: definition of intellectual contents, manuscript preparation and editing. Khandagale AS: definition of intellectual contents, data analysis, manuscript preparation and editing. Bapu AB: data analysis and statistical analysis. Sadashiv R: definition of intellectual content, manuscript editing and manuscript review. Reddy P: manuscript editing and manuscript review and manuscript review.

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RESUMO – Contexto – O carcinoma colorretal (CCR) é um dos carcinomas comuns com incidência crescente de metástases devido ao seu estágio avançado de apresentação. Os biomarcadores existentes como CEA (antígeno carcinoembrionário) etc., para prognóstico, apresentam baixa sensibilidade e especificidade. Daí a necessidade de um biomarcador definitivo mais recente. A obesidade é a principal causa do CCR. A leptina e a adiponectina secretadas pelo tecido adiposo têm sido estudadas como potenciais biomarcadores na área do CCR. O presente estudo ajuda a compreender a associação dos receptores de leptina e adiponectina com parâmetros clinicopatológicos. **Objetivo** – Correlacionar os diversos parâmetros clinicopatológicos com a expressão tecidual dos receptores de leptina e adiponectina no CCR. **Métodos –** Trata-se de um estudo transversal, prospectivo, realizado em um hospital terciário. Blocos de parafina fixados em formalina de todos os casos de CCR de ressecção radical foram coletados e a imuno-histoquímica (IHQ) foi realizada no tecido tumoral para receptor de leptina e adiponectina. As características do tumor e os parâmetros clínicos foram coletados dos prontuários médicos do hospital. Foi utilizado o teste do coeficiente de correlação de Pearson. **Resultados** – A imunohistoquímica foi realizada em 60 casos de CCR. Correlação positiva significativa da leptina foi observada com tamanho e metástase linfonodal, estágio avançado e grau do tumor (P<0,01). Foi observada uma correlação significativa entre o receptor de adiponectina e o CCR em relação à idade, estágio, metástase linfonodal, metástase à distância e grau do tumor. **Conclusão** – A expressão positiva de leptina e a expressão negativa de receptores de adiponectina no CCR ajudam a prever o risco de metástase.

Palavras-chave – Carcinoma colorretal; leptina, receptor de adiponectina; imuno-histoquímica.

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