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Research Article

Role of Kisspeptin-1 and Growth Differentiation Factor-15 in Iraqi Patients with Metastatic and Non-metastatic Colorectal Cancer

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer mortality worldwide. Identifying novel biomarkers is critical for improving diagnosis, prognosis, and treatment strategies. This study investigates the serum levels of kisspeptin-1 (KISS1), its receptor (KISS1R), growth differentiation factor 15 (GDF15), and carcinoembryonic antigen (CEA) in Iraqi CRC patients. ***Objectives***: Explore associations between serum levels of Kiss1, Kiss1R, GDF, and CEA and disease progression in Iraqi patients with CRC. ***Methods***: A case-control study was conducted, including 72 CRC patients and 36 healthy controls. Patients were stratified into non-metastatic and metastatic groups. Serum biomarker levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses evaluated biomarker correlations, diagnostic accuracy, and associations with CRC stages. ***Results***: Significant elevations of KISS1, KISS1R, GDF15, and CEA levels were observed in CRC patients compared to controls, with metastatic cases showing the highest levels. KISS1 and GDF15 demonstrated strong correlations and were particularly associated with metastatic disease. Receiver operating characteristic (ROC) analysis revealed high diagnostic accuracy for these biomarkers in distinguishing CRC stages. ***Conclusions***: KISS1 and GDF15 are promising biomarkers for CRC progression and metastasis. Their coordinated elevation in metastatic cases suggests potential roles in disease monitoring and therapeutic targeting. Further studies are needed to confirm these findings and explore their clinical applications.

Keywords: Carcinoembryonic antigen, Colorectal cancer, Growth differentiation factor-15, Kisspeptin-1, Kisspeptin-1 receptor.

دور كيسبيبتين -1 وعامل تمايز النمو -15 في المرضى العراقيين المصابين بسرطان القولون والمستقيم النقيلي وغير النقيلي

الخلاصة

الخلفية: سرطان القولون والمستقيم (CRC) هو سبب رئيسي للوفيات الناجمة عن السرطان في جميع أنحاء العالم. يعد تحديد المؤشرات الحيوية الجديدة أمرا بالغ الأهمية لتحسين استراتيجيات التشخيص والعلاج. تبحث هذه الدراسة في مستويات مصل كيسبيبتين 1 (KISS1)، ومستقبلاته (KISS1R)، وعامل تمايز النمو 15 (GDF15)، والمستضد السرطاني الجنيني (CEA) في مرضى سرطان القولون والمستقيم العراقيين. **الأهداف**: استكشاف الارتباطات بين مستويات مصل Kiss1 و Kiss1R و GDF و CEA وتطور المرض لدى المرضى العراقيين المصابين بسرطان القولون والمستقيم. **الطرائق**: أجريت دراسة حالة وشواهد، شملت 72 مريضا بسرطان القولون والمستقيم و36 ضابطا صحيا. تم تقسيم المرضى إلى مجموعات غير نقيلية ونقيلية. تم قياس مستويات المؤشرات الحيوية في المصل باستخدام مقايسة الممتز المناعي المرتبط بالإنزيم (ELISA). قيمت التحليلات الإحصائية ارتباطات المؤشرات الحيوية ودقة التشخيص والارتباطات بمراحل CRC. **النتائج**: لوحظت ارتفاعات كبيرة في مستويات KISS1 و KISS1R و GDF15 و CEA في مرضى CRC مقارنة بالضوابط، حيث أظهرت الحالات النقيلية أعلى المستويات. أظهر KISS1 و GDF15 ارتباطات قوية وارتبطتا بشكل خاص بالمرض النقيلي. كشف تحليل خصائص تشغيل المستقبل (ROC) عن دقة تشخيصية عالية لهذه المؤشرات الحيوية في تمييز مراحل CRC. **الاستنتاجات**: KISS1 و GDF15 هي مؤشرات حيوية واعدة للكشف عن تطور سرطان القولون و المستقيم و الكشف عن النقائل. يشير ارتفاعها المنسق في الحالات النقيلية إلى أدوار محتملة في مراقبة المرض والاستهداف العلاجي. هناك حاجة إلى مزيد من الدراسات لتأكيد هذه النتائج واستكشاف تطبيقاتها السريرية.

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INTRODUCTION

Colorectal cancer (CRC) has become increasingly prevalent, with 1.9 million new cases and 0.9 million deaths reported globally in 2020, making it the third leading cause of cancer mortality [1]. Current treatments for metastatic colorectal cancer are considered palliative. These treatments have significantly improved the progression-free survival of patients with metastatic CRC, which ranges from 22 to 29 months [2]. Since CRC is a heterogeneous disease, there is a critical need for the discovery of novel biomarkers to identify patients who will most likely benefit from treatment [3]. Kisspeptins, a family of peptides that include kisspeptin-54 (also known as metastin), kisspeptin-14, kisspeptin-13, and kisspeptin-10, act through a G protein-coupled

receptor identified as KISS1R or GPR54, belonging to the Gq/11 subfamily [4,5]. Kisspeptins play a critical role in regulating the metastatic potential of malignant cells, acting to inhibit cell migration, metastasis, and invasion of surrounding tissues, as well as to suppress angiogenesis and cell proliferation and to promote apoptosis [6]. Extensive research has explored the function of kisspeptins across multiple cancers, including melanoma and cancers of the esophagus, stomach, liver, pancreas, lung, thyroid, breast, ovary, endometrium, and bladder, as well as in choriocarcinoma, osteosarcoma, and pheochromocytoma [7]. Many findings indicate that KISS1 expression is often lower in malignant tissues compared to normal tissue and that kisspeptin levels tend to decline in advanced cancer stages, although some studies report differing results [8]. Research specifically investigating KISS1's role in colorectal cancer, however, remains limited [8]. On the other hand, the circulating inflammatory cytokine growth differentiation factor GDF15 belongs to the BMP subfamily within the TGF-β superfamily. It is expressed across various mammalian tissues and plays diverse roles in conditions like inflammation, cancer, cardiovascular disease, and obesity but is not yet fully interpreted [9]. Elevated circulating GDF15 levels have been observed in cancers such as endometrial [10], prostate [11], pancreatic [12], and colorectal cancer [13], where these elevations are often associated with unfavorable clinical outcomes. While the exact function of GDF15 in tumorigenesis remains complex and, at times, inconsistent, in CRC, GDF15 has been identified as a negative prognostic marker, with high GDF15 levels in both tumor tissue and plasma linked to increased recurrence risk and decreased overall survival [13,14]. This study evaluated serum levels of Kiss1, Kiss1R, and GDF, along with CEA, in a sample of Iraqi patients with CRC across various disease stages. The objective was to explore potential associations between these markers and the progression of disease stages.

METHODS

Study design and setting

This case-control was conducted in the Oncology Teaching Hospital, Medical City, Baghdad to evaluate serum levels of specific biomarkers in colorectal cancer (CRC) patients at various stages of the disease compared to healthy controls. The study was carried out in accordance with the principles of the Helsinki Declaration and its appendices and with local and national laws. Approval was obtained from the hospital's Internal Review Board and its Ethics Committee, and written informed consent was obtained from all patients.

Inclusion and exclusion criteria

Patients with CRC included both males and females with a confirmed pathohistological diagnosis of colorectal cancer (stage I to IV). Exclusion criteria included patients with primary cancers in other organs metastasizing to the colon, inflammatory bowel disease such as Crohn's disease, ulcerative colitis, liver diseases, autoimmune disorders, and those who were pregnant or lactating.

Participants and sample collection

A total of 72 patients diagnosed with CRC, aged between 20 and 80 years, participated in the study. Diagnosis of CRC was confirmed through a combination of clinical evaluation, imaging studies (e.g., colonoscopy with biopsy), and histopathological analysis, in accordance with standard diagnostic protocols. The study participants were stratified based on disease progression using the American Joint Committee on Cancer (AJCC) staging system, ranging from stage I to IV [15]. The cohort included two groups of CRC patients: Group 1 comprised 36 individuals without metastatic disease, while Group 2 consisted of 36 individuals with metastasis. Additionally, a control group (Group 3) included 36 healthy individuals with no history of CRC or other exclusionary conditions, serving as the reference population. Blood samples were collected from each participant to obtain serum, which was subsequently analyzed for levels of kisspeptin-1, kisspeptin receptor (KISS1R), GDF15, and carcinoembryonic antigen (CEA).

Biomarker analysis

Serum levels of Kisspeptin-1, KISS1R, GDF15, and CEA were measured using specific enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's HumaReader HS protocols for each assay.

Statistical analysis

The data were analyzed using IBM SPSS Statistics software. One-way analysis of variance (ANOVA) was employed to compare biomarker levels, including kisspeptin-1, KISS1R, GDF15, and CEA, across G1, G2, and G3. For cases where the assumptions of ANOVA were not met, a non-parametric Kruskal-Wallis test was utilized. Post-hoc tests or pairwise comparisons were conducted to identify specific group differences where a significant variance was observed. Correlation analysis was performed to evaluate relationships between biomarker levels and CRC stages. All statistical tests were two-tailed, with a significance threshold set at $p < 0.05$.

RESULTS

The demographic characteristics of the study population in Table 1 revealed two groups of (CRC) patients: non-metastatic (Group 1) and metastatic (Group 2), alongside a healthy control group (Group 3). Both CRC groups showed male predominance, particularly in group 2 (72.2%). Most patients were classified as tumor stage T3 (63.9% in group 1, 69.4% in group 2), with variable lymph node involvement. Tumors were primarily located in the colon (63.9% in group 1, 66.7%

in Group 2), with equal left and right colon distribution in group 2 (33.3% each). The liver was the predominant site of metastasis (69.4%, n=25), followed by isolated lung (19.4%, n=7) and combined liver and lung metastases (11.1%, n=4).

Table 1: Demographic characteristics of the groups studied

Parameter		Group 1	Group 2	Group 3
Sex	Female	16(44.4)	10(27.8)	21(58.3)
	Male	20(55.6)	26(72.2)	15(41.7)
Non-Parametric parameters		**Sub-classes**	**Study groups**	
			1	**2**
T		2	4 (11.1)	0(0.0)
		3	23(63.9)	25(69.4)
		4	9(25.0)	11(30.6)
N		0	10(27.8)	0(0.0)
		1st	18(50.0)	26(72.2)
		2nd	8(22.2)	10(27.8)
M		No	36(100)	0(0.0)
		Yes	0(0.0)	36(100)
Site of cancer		Colon	23(63.9)	24(66.7)
		Rectum	13(36.1)	12(33.3)
Location of cancer in the colon		Left	10(27.8)	12(33.3)
		Right	13(36.1)	12(33.3)
Grade of the disease		A	2(5.6)	1(2.8)
		B	33(91.7)	30(83.3)
		C	1(2.8)	5(13.9)
Metastases		Liver	0(0.0)	25(69.4)
		Liver ang lung	0(0.0)	4(11.1)
		Lung	0(0.0)	7(19.4)

Values were expressed as number and percentage. Group 1: Non-metastatic CRC patients; Group 2: Metastatic CRC patients; Group 3: Healthy controls; T: Tumor size; N; Lymph node involvement; M: Metastasis.

Table 2 demonstrates that for each tumor marker analyzed—GDF, KISS, KISSR, and CEA—significant differences were observed across the studied groups. Table 2 shows that the mean levels of GDF were 307.37, 405.64, and 38.85 for group 1, group 2, and group 3, respectively. Similarly, the KISS marker demonstrated mean levels of 382.27, 526.41, and 198.57, respectively, demonstrating higher levels in the metastatic group compared to both the non-metastatic and control groups. The mean value of KISS1R and CEA is also shown in Table 2.

Table 2: : Serum levels of GDF, KISS-1, KISS-1R and CEA in the studied patients and controls (n=36 in each group)

Marker	Groups	Result	*p*-value
GDF (pg/ml)	Group 1	307.37±12.43	0.017[a]
	Group 2	405.64±15.85	<0.001[b]
	Group 3	38.85±2.22	<0.001[c]
KISS (ng/ml)	Group 1	382.27±1.87	0.021[a]
	Group 2	526.41±13.8	<0.001[b]
	Group 3	198.57±4.29	<0.001[c]
KISSR (nmol/l)	Group 1	6.01±0.18	0.003[a]
	Group 2	7.03±2.22	<0.001[b]
	Group 3	1.68±0.04	<0.001[c]
CEA (ng/ml)	Group 1	3.27±0.17	0.014[a]
	Group 2	4.56±0.26	<0.001[b]
	Group 3	0.89±0.06	<0.001[c]

Values were expressed as mean±SD. Group 1: Non-metastatic CRC patients; Group 2: Metastatic CRC patients; Group 3: Healthy controls. [a] significant difference between groups 1 and 2; [b] significant difference between groups 2 and 3; [c] significant difference between groups 1 and 3.

Table 3 highlights the correlations among tumor markers within each disease group. Notably, KISS1 exhibited a positive correlation with CEA (r= 0.787, p< 0.001), GDF (r = 0.907, p< 0.001), and KISS1R (r = 0.779, p< 0.001). Tables 4 and 5 reveal distinct biomarker correlation patterns between group 1 and group 2. In group 2, KISS1 demonstrated strong correlations with GDF (r = 0.715, p< 0.001), along with a significant positive correlation between GDF and CEA (r = 0.413, p = 0.01). In contrast, group 1 exhibited a significant correlation only between KISS1 and GDF (r = 0.792, p< 0.001).

Table 3: Pearson's correlation between the markers studied among the groups

Markers	Analysis	Result
KISS1 *vs*. CEA	*r*	0.787
	p	<0.001
KISS1 *vs*. GDF	*r*	0.907
	p	<0.001
KISS1 *vs*. KISS1R	*r*	0.779
	p	<0.001
GDF *vs*. CEA	*r*	0.859
	p	<0.001

Table 4: Pearson's correlation between markers within group 1

Marker	Analysis	Result
KISS1 *vs*. CEA	*r*	0.081
	p	0.64
KISS1 *vs*. GDF	*r*	0.792
	p	<0.001
GDF *vs*. CEA	*r*	0.267
	p	0.116

Table 5: Pearson's correlation between markers within group 2

Marker	Analysis	Result
KISS1 *vs*. CEA	*r*	0.225
	p	0.187
KISS1 *vs*. GDF	*r*	0.715
	p	<0.001
GDF *vs*. CEA	*r*	0.413
	p	0.01

Table 6 explores the relationship between KISS1 and TNM classification, revealing no significant correlation with tumor size (T) or lymph node involvement (N). However, there was a notable association between serum level of KISS1 and metastasis (M) ($r = 0.579$, $p < 0.001$), indicating a possible link between serum KISS1 levels and the metastatic status of CRC.

Table 6: Pearson's Correlation between KISS-1 and TNM Classification

Marker	Analysis	Result
KISS1 *vs*. T	*r*	0.19
	p	0.874
KISS1 *vs*. N	*r*	0.05
	p	0.674
KISS1 *vs*. M	*r*	0.579
	p	<0.001

T: Tumor size; N; Lymph node involvement; M: Metastasis.

DISCUSSION

Despite significant progress in the diagnosis and prognosis of colorectal cancer (CRC), the identification of enhanced biomarkers remains critical for early detection and improved outcome prediction. Our study provides a comprehensive evaluation of emerging tumor markers in CRC, focusing on their potential clinical validity with minimally invasive nature. Specifically, we assessed the levels of Kisspeptin 1, Kiss receptor (KISS1R), and GDF15 within our study population, comparing these markers with the established carcinoembryonic antigen (CEA) marker. In our analysis, GDF15 levels were notably higher in patients with metastatic CRC than in those without metastasis, with substantially lower levels in the control group. Consistent with our results, a multinational multicenter meta-analysis reported elevated serum GDF15 levels in CRC patients compared to healthy controls, with a diagnostic sensitivity of 58.9%, specificity of 92.08%, and an AUC of 0.816, supporting GDF15's strong diagnostic performance in CRC. [16]. Another controlled study in Egypt has found significantly higher median levels of serum GDF15 among CRC patients compared to controls [17]. Those findings underscore GDF15's potential as a robust tumor marker for CRC, not only for diagnostic and screening purposes but also as a possible prognostic tool. Our findings also revealed elevated median serum Kiss1 levels in CRC patients (373.90) relative to controls, with even higher levels in patients with metastatic disease (489.77). In a related study, Canbay et al. found that plasma Kisspeptin-54 levels were significantly higher in early-stage CRC patients than in controls, suggesting that Kisspeptin may serve as a serum tumor marker for non-metastatic CRC [18]. Similarly, both KISS1R and CEA levels exhibited higher medians in the metastatic group compared to non-metastatic and control groups. Notably, a study identified a significant correlation between reduced KISS1 and KISS1R expression and poorer overall survival in patients with colorectal liver metastasis ($p < 0.05$), with low KISS1 expression being an independent prognostic factor, particularly associated with distant metastasis ($p < 0.05$) [19]. It was discovered that GDF15 facilitates metastasis in colorectal cancer (CRC) by promoting a process called epithelial-to-mesenchymal transition (EMT). This happens when GDF15 activates Smad2/3 signaling by connecting to TGF-β receptors. Elevated GDF15 levels in tissue and serum correlate with reduced survival rates and are more sensitive than CEA for early CRC detection and hepatic metastasis [20]. Our study found that the significant correlation between KISS1 and GDF ($p = 0.000$) in metastatic and non-metastatic CRC cases suggests a possible coordinated elevation of these markers as an early cancer response, potentially working to inhibit initial tumor spread and highlighting a dynamic interaction as the disease progresses. Those findings are supported by the conclusion of a genetic study by Zhou *et al*., where they found that GDF15 translocation to the nucleus has been shown to modulate gene expression, including that of KISS1, ultimately inhibiting cellular proliferation and invasiveness [21]. Notably, to mention that we found there is no significant association between KISS1 and CEA ($p = 0.64$) in non-metastatic patients, indicating that such relationships may emerge only in the presence of metastasis. We studied how KISS1 levels relate to TNM staging in colorectal cancer (CRC) patients. Our findings show that KISS1 does not have a significant link to tumor size (T) or lymph node involvement (N), but it does show a significant connection with metastasis (M). This finding suggests that KISS1 may play a crucial role specifically in the metastatic progression of CRC rather than in the initial tumor growth or regional lymphatic spread. The strong association between KISS1 and metastasis underlines the gene's function as a metastasis suppressor and may indicate its potential utility as a biomarker for identifying metastatic risk in CRC patients. In another study, Ji *et al*. analyzed KISS1 and KISS1R transcript levels in 94 colorectal cancer tissue samples and 80 normal tissues. They observed that KISS1 expression was inversely correlated with Duke's stage, TNM stage, tumor size, and lymph node involvement, indicating that lower KISS1 levels were associated with more advanced disease features. Similarly, reduced KISS1R expression was linked to a poorer prognosis for patients [22]. These results support further exploration of KISS1 as a prognostic marker, particularly for its potential to inform clinical decisions regarding metastatic monitoring and treatment strategies in CRC management. AUC values exceeding 0.9 for GDF15, KISS, and KISSR; these markers demonstrated exceptional accuracy in differentiating CRC stages. These results collectively emphasize the clinical utility of these biomarkers in enhancing the diagnostic precision and staging accuracy for CRC patients.

Study Limitations

This study includes a few limitations. First, the relatively small sample size may limit the generalizability of findings to the broader CRC population. Additionally, the single-center study design may limit the applicability of results to other populations

and healthcare settings. Future studies should include larger, multicenter cohorts to confirm these findings and enhance the external validity of the results. Longitudinal studies would be beneficial in establishing causal relationships between KISS1, GDF15, and CRC progression. Additionally, further exploration of the molecular mechanisms linking KISS1 and GDF15 in CRC is warranted, as well as evaluating their utility as biomarkers for early detection and therapeutic targets.

Conclusion

This study reveals that serum levels of KISS1, KISS1R, GDF15, and CEA show distinct patterns across different stages of colorectal cancer (CRC), particularly highlighting the role of KISS1 and GDF15 in distinguishing metastatic and non-metastatic CRC cases. Elevated serum levels of KISS1 and GDF15 in patients with metastatic CRC suggest these markers as potential indicators for disease progression. The significant correlation between KISS1 and GDF15 also points to their possible coordinated role in tumor progression, making them promising targets for further investigation as biomarkers for CRC prognosis and therapeutic response.

Conflict of interests

No conflict of interest was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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