Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with over 1.2 million new cancer cases and 608700 estimated deaths in 2008 (Tandon et al., 2015).

It’s also the third most common cancer worldwide after lung and breast cancers. It is two-thirds of all cancers occurring in the developed regions of the world. It affects men and women of all racial and ethnic groups (Gado et al., 2013). In Egypt, GLOBOCAN 2012 showed that colorectal cancer considered the 8th cancer after breast, liver, non-Hodgkin lymphoma, brain, ovary, leukemia and bladder cancer with incidence rate account for 4 % and 3.5 % for men and women respectively. With a mortality rate of 3.5 % and 3.8 % in men and women respectively. Many epidemiologic studies have shown a positive correlation between obesity, increased risk of colorectal cancer and adenoma, in accordance with the International Agency for Cancer Research (IACR), besides other cancers at various sites (e.g. breast, prostate gland, and endometrium) (Nakajima et al., 2010; Fazeli et al., 2013).

During the last two decades, fat tissue has become gradually observed not only as an energy storage depot...
but also as an active endocrine organ that produces and secretes proteins acting as hormones called adipocytokines or adipohormones (Kumor et al., 2009; Akdogan et al., 2014).

Adipocytokines are protein factors that show a number of important systemic complex interactions and influence a large number of different organ systems (Schaffler et al., 2005).

Numerous adipocytokines, namely adiponectin, visfatin and resistin have been under investigation in a multitude of robust in vitro (Yamaji et al., 2010; Fazeli et al., 2013).

Adiponectin is an adipokin product of mature adipocyte, and is known to be reduced in the case of insulin resistance, positively correlated with insulin sensitivity and affect weight loss (Becarevic et al., 2012). It regulates intracellular pathways of protein kinase activated by AMP (AMP-kinase), of c-JUN, c-JUN N-terminal kinase (JNK) and of the signal that transcribes and activates transcription 3 (STAT3) and nuclear factor kappa-B by inhibiting IL-6 and TNF-α (Joshi and Lee, 2014). Adiponectin may have anti-tumor effect through a pro-apoptotic and anti-angiogenic pathway, as several studies showed inverse correlation between adiponectin and various kinds of cancer (Phillip et al., 2011). Many studies showed decreased level of adiponectin is a strong risk factor for early CRC (Otaka et al., 2010; Fazeli et al., 2013).

Resistin, which is an insulin resistance-inducing factor, is a signaling molecule secreted from adipocytes and monocytes, it has recently been shown to be involved in inflammatory processes including atherosclerosis and some human cancers. Resistin levels correlate with various cancers including colorectal, prostatic and endometrial cancers (Dalamaga et al., 2009, Gan et al., 2013). Resistin, like visfatin, exerts potent pro-inflammatory properties by upregulating pro-inflammatory cytokines, most likely via the nuclear factor kappa-B (NFkB) pathway, suggesting resistin is involved in the process of inflammation (Gonullu et al., 2010; Lee et al., 2012; Tulubas et al., 2013).

Visfatin, which is secreted by visceral fat, is a new adipokine that is structurally identical to pre-B-cell colony-enhancing factor (PBEF) and exhibits nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity (Dalamaga et al., 2012; Tulubas et al., 2013).

Elevated circulating levels of visfatin have been found in patients with metabolic disorders, such as diabetes mellitus, obesity or metabolic syndrome (MS), which might be related to the development of MS-related cancers (Słomian et al., 2014).

So, in this study we aimed to evaluate the levels of (Adiponectin, Resistin and Visfatin) in pre-malignant and malignant colorectal lesions for early detection to understand the possible role of adipocytokines in relation to disease progression and early detection of colorectal cancer.

Materials and Methods

Study population

The current study was conducted on 114 adult patients divided into four groups: group 1 colorectal cancer (CRC; n = 34), colonic polyps (CP; n = 27), inflammatory bowel disease (IBD; n = 24) and control group (n = 29) with different colonic symptoms but with no abnormality detected at their colonoscopic examination, so they were enrolled in this study as a control group attending the gastrointestinal endoscopy unit of the tropical medicine department, Kasr El Aini hospital, faculty of medicine, Cairo University and Egypt Air hospital in the period from January 2011 to March 2012. The study was approved by the Investigation and Ethics Committee of the hospital and a written consent was obtained from all the persons involved. All the patients and control enrolled in this study almost have same body mass index.

A detailed history, clinical assessment, complete blood picture, occult blood and colonoscopic examination were done to all study groups in addition to histopathological examination. Collection of clinical specimens: 5 ml of venous blood was left to coagulate, and then centrifuged at 5000 rpm for 10 minutes. Serum was collected after a second centrifugation and then stored at -80OC until used.

Adipocytokine measurements

Serum levels of adiponectin, resistin and visfatin were measured by a commercially available ELISA kit from (RayBiotech, USA), according to the manufacturer’s instructions.

Statistical analysis

Quantitative variables were expressed by median and interquartile ratio (IQR) for non-parametric data. They were compared by Mann- Whitney U test for 2 groups or Kruskal- Wallis for more than 2 groups. ROC curves were constructed to assess reliability of the new marker in detection of CRC lesions.

Sensitivity and specificity were calculated in relation to best cutoff value obtained from the curve. All p-values are two-sided. P-values <0.05 were considered significant.

<table>
<thead>
<tr>
<th>CONTROL</th>
<th>IBD</th>
<th>CP</th>
<th>CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>mean 43.07±2.79b</td>
<td>41.67±3.2b</td>
<td>40.04±2.84b</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>16 (59.3 %)</td>
<td>17 (70.8 %)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>11 (40.7 %)</td>
<td>7 (29.2 %)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>mean 10.78±2.16b</td>
<td>10.7±1.4b</td>
<td>10.3±1.42b</td>
</tr>
<tr>
<td>TLC</td>
<td>mean 23.48±18.8b</td>
<td>51.04±27.86b</td>
<td>51.29±34.55b</td>
</tr>
<tr>
<td>Platelets</td>
<td>mean 219080±85135a</td>
<td>179443.48±58330a</td>
<td>305110.7±50847a</td>
</tr>
</tbody>
</table>

P-value is considered significant if <0.05, groups bearing different initials significantly different

Table 1. Clinical Characteristics of Studied Patients

Results

Clinical characteristics of the studied patients as well as the Histopathological types of the colonic biopsies are shown in Table 1 and Table 2 respectively.

Detailed clinical data of all studied groups are shown in Table (1). The clinical data showing that our study is retrospective age and sex case controlled where there is no significant difference between studied groups in age and sex.

There is significant decrease in hemoglobin level in CRC group compared to control group (p-value = 0.04) where total leucocyte count was highly elevated in IBD groups compared to other groups (p-value = 0.026). ESR is significantly highly elevated in all groups compared to control group (p-value < 0.001).

The levels of studied biomarkers in the different groups were expressed as scatter plot in Figure (1), as box plot showing biomarkers distribution in Figure (2) and as mean ±SD beside median in Table (3). The mean concentration of adiponectin was significantly higher in CRC and CP groups than IBD and control groups (P-value<0.05) with mean values 11280±1499, 11125±1635, 2782±614 and...
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6591±1745 respectively. Also the mean concentration of serum resistin was significantly elevated in the IBD and control groups compared to CRC and CP groups with mean values 35216±5788, 29661±3204, 20824±3620 and 19240±2454 respectively (P-value = 0.014). However, no significant difference was noticed in patients with CRC and CP groups. On the other hand, the mean concentration visfatin was significantly elevated in CRC and control groups compared to CP and IBD groups with mean values 5.12±1.17, 6.58±1.35, 2.09±0.31 and 3.59±0.49 respectively (P-value = 0.03).

Further analysis of the data using Receiving Operating Characteristic (ROC) analysis curves and the corresponding area under the curve were attempted for the studied markers to investigate accuracy between different groups demonstrating cut off values with their specificity, sensitivity, +LR (positive likelihood ratio) and -LR (negative likelihood ratio) as shown in Table (4) & Figure (3). It has been shown that between CRC and IBD groups serum level of adiponectin had a sensitivity of 76.7% and specificity of 76% at cut off value of 3940, +LR was 3.2 and -LR was 0.31 with AUC 0.852, while serum level of adiponectin between CP and IBD had sensitivity of 77.8% and specificity of 75% at cut off value of 3300, with +LR=3.11 and -LR = 0.3 with AUC 0.852. On the other hand serum level of visfatin between CRC and CP group had a sensitivity of 65.5% and the specificity of 66.7% at cut off value of 2.4, +LR was 1.67, -LR = 0.52 with AUC 0.698. Also Serum level of resistin had a sensitivity of 62.5% and specificity of 70.3% at cut off value of 24500, with +LR=2.1 and -LR = 0.53 with AUC 0.685 between control and other groups. On the other hand by comparing control against CP groups resistin had sensitivity of 81.8% and specificity of 70.8% at cut off value of 17700, with +LR=2.8 and -LR = 0.26 with AUC 0.763 while visfatin had sensitivity of 68.2% and specificity of 70.8% at cut off value of 2.7, with +LR=2.34 and -LR = 0.0.45 with AUC 0.812.

Discussion

Colon cancer comes third among the most common types of cancer (MJ 2002; Akdogan et al., 2014). Adipokytokines produced by adipose tissue have been investigated as new risk factors for cancer and metabolic syndromes (Nakajima et al., 2010; Akdogan et al., 2014). The aim of our study is to evaluate the levels of adipokytokines (Adiponectin, Resistin and Visfatin) as potential biomarkers for early detection of Egyptian colorectal carcinoma patients. So we measured the levels
Circulating Levels of Adipocytokines as Potential Biomarkers for Early Detection of Colorectal Carcinoma in Egyptian Patients

Akdogan R, Ozgur O, Gucuyeter S, et al (2014). A pilot study of Helicobacter pylori genotypes and cytokine gene expression as mentioned by (Kralisch et al., 2005) who proposed that TNF-α suppress visfatin gene expression in dose- and time-dependent manner. Serum level of visfatin between CRC and CP group had a sensitivity of 65.5% and the specificity of 66.7 at cut off value of 2.4, +LR was 1.67, -LR was 0.52 with AUC 0.7, while by comparing visfatin levels between control vs CP groups it had sensitivity of 68.2% and specificity of 70.8% at cut off value of 2.7, with +LR=2.34 and -LR = 0.0.45 with AUC 0.812.

Resistin, also named ADSF (adipocyte secreter factor) is a member of RELMs (resistin-like molecules) family protein with cysteine rich structure. It is identified as a 12.5 kDa polypeptide related to human chromosome 19 (Ghaemmaghami et al., 2013).

Resistin level was highly elevated in IBD group compared to other groups, this result in agreement with (Stofkova., 2010), (Axelsson J, Bergsten A, Qureshi AR 2006) and many others who reported that resistin plasma level is increased in many inflammation related disorders such as atherosclerosis, chronic inflammatory bowel disease, chronic renal disease, systemic lupus erythematosus (SLE), arthritis.

Resistin mRNA expression has been demonstrated to be enhanced by peripheral blood mononuclear cells (PBMCs) stimulation with endotoxin or pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α (Kaser S, Kaser A, Sandhofer A 2003), this results in concordance with our postulation of elevated TNF-α which causes the elevation of resistin in IBD group.

On the other hand no significant difference was noticed between CRC and control group this is due to the chronic low grade inflammation status in CRC (Ghaemmaghami et al., 2013)

Serum level of resistin had sensitivity of 62.5% and specificity of 70.3% at cut off value of 24500, with +LR=2.1 and -LR = 0.53 with AUC 0.69 with poor diagnostic accuracy as AUC was in the range of (0.7-0.79), between control and other groups. On the other hand by comparing control vs CP groups resistin had sensitivity of 81.8% and specificity of 70.8% at cut off value of 2.7, with +LR=2.34 and -LR = 0.0.45 with AUC 0.812.

Further investigation is needed to measure TNF-α in the different groups to study its real mechanism in the effect of the studied markers in the different groups of patient

References


