Type-II Endometrial Cancer – Role of Adipokines

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Abstract:

**Background:** Type II Endometrial cancer is an estrogen independent and one of the most lethal types of cancer having poor prognosis. Adipokines play a crucial role in the triggering Type-II EMC. And adipokines modulators, therefore, may have beneficial effects in the treatment of Type-II endometrial cancer, which was clinically evidenced.

**Areas covered:** This review presents the role of various adipokines involved and also the suitable modulators to treat Type-II endometrial cancer.

**Conclusion:** In the present review we try to discuss the role of individual adipokines in the pathogenesis of Type-II endometrial cancer, and also the possible beneficial effects of adipokines modulator in the treatment of Type-II endometrial cancer.

**Keywords:** Endometrial cancer, Adipokines, Adiponectin, Leptin, Visfatin, Resistin, Adipokine modulators, cancer, Type-II EMC
Endometrial cancer (EMC) is considered to be one of the most common disease of the female uterus [1]. As per the National Cancer Institute, USA, 3.6% increase in the occurrence of EMC was recorded over a period of last 10 years (2008-2018) [2]. The etiological factors reported to cause EMC include obesity, diabetes mellitus, polycystic ovarian syndrome, estrogen-producing tumours, menopause, excessive levels of estrogen and age-related factors [3, 4]. EMC is of 2 types where, Type-I is characterized by unopposed estrogen stimulation resulting in a low-grade histology and it is often found in association with atypical endometrial hyperplasia [2–6]. The gene reported to be most commonly associated with the Type-I EMC is AT-rich interactive domain-containing protein 1A (ARID1A) [7, 8]. Mutations in Phosphoprotein53 (p53) gene, Phosphatase and Tensin homolog (PTEN) and Phosphatidylinositol-4,5-bisphosphate3-kinase catalytic subunit alpha isoform (PIK3CA) is observed in both the types of EMC [7, 9]. Serious carcinoma is one of the Type-II EMC and one of the worst prognosis and is oestrogen independent [10–12].

The pathophysiology of Type-II EMC involves alterations in the function of tumour suppressor genes p53, PTEN and oncogene like Phosphoinositide3-kinase (PI3K), Protein kinase B (Akt) and mammalian target of rapamycin (mTOR) [5, 9, 13]. The most common genetic alteration occurs in p53, which leads to inhibition of apoptosis and uncontrolled proliferation of cells of endometrium [5, 14–17].

Similarly, loss of function in PTEN also leads to inhibition of Phosphatidylinositol 3-phosphate (PIP3), thereby escaping the apoptosis (proliferation by up-regulation of PI3K,mTOR and Akt pathway) (Figure-1) [18–28]. However, overexpression of oncogenes like Kirsten rat sarcoma 2 viral oncogene homolog (KRas), B-catenin, and Human epidermal growth factor receptor2 (Her2) causes excess proliferation of cells of endometrium (Figure-1)
The KRas stimulates cell proliferation by Mitogen-activated protein kinase (Raf-MEK) pathway, whereas the B-catenin and Her2 damages the DNA causing cell growth and survival (Figure-1) [17, 24]. Recent studies have shown that the risk of occurrence of EMC is 2.5 to 3 times more in patients with obesity and, this may be related to the increased levels of adipokines in the obese patients, which are reported to activate several pathways involved in the pathogenesis of EMC [34–39]. Adipokines like Leptin, Visfatin, Resistin, Interleukine-6 (IL-6), Interleukine-8 (IL-8), Insulin growth factor-1 (IGF-1) and Sex hormone binding globulins, are reported to activate pathways such as Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kβ) and mTOR, leading to Type-II EMC (Figure-1) [25, 40]. In this review article an attempt has been made to shed light on the role of adipokines in the pathogenesis of Type-II EMC.
Role of Adipokines

Adipokines are active metabolic molecules secreted by adipose tissue. Important adipokines include Leptin, Visfatin, Resistin, Adiponectin, IL-6, Tumor Necrosis Factor Alpha (TNF-α),
Apelin, Chimerin, Monocyte Chemotactic Protein -1 (MCP-1), Plasminogen Activator Inhibitor-1 (PAI-1), Retinol Binding Protein-4 (RBP4), Omentin, Progranulin, Vaspin and Compliment C1q tumour necrosis factor related protein-4 (CTRP-4) [5, 41–43]. A significant correlation has been reported between the occurrence of Type-II EMC and the obesity [44–46]. Among the different adipokines Leptin, Resistin, and Visfatin are reported to promote the occurrence of Type-II EMC by activation of NF-kβ and mTOR pathways[47]. Whereas, Adiponectin is reported to prevent the occurrence of Type-II EMC by activating AMP-activated protein kinase (AMPK) pathway and thereby, inhibiting mTOR (Figure-2) [11, 48]. Adipokines like IL-6 and TNF-α were reported to activate STAT3 and NF-kβ pathways, respectively, and promote cancer cell survival, proliferation and metastasis [49–51]. MCP-1 and Progranulin are reported to promote angiogenesis and tumor progression through activation of macrophages and release of IL-8 respectively [52, 53]. Omentin is reported to promote genomic instability of signalling proteins in P13K/Akt pathways, resulting in increased cell proliferation [54–56]. Vaspin inhibits various pathways like Reactive Oxygen Species (ROS), MAPK and P13K/Akt which inturn reported to promote carcinogenesis [57]. However, their exact role at the molecular level still needs to be understood. From the above findings it is clear that Leptin, Resistin, and Visfatin adipokines promote Type-II EMC and Adiponectin is reported to prevent Type-II EMC (Figure-2) [44].
Figure-2: Role of Adipokines in Type-II EMC: Adipokines (except Adiponectin) activates various pathways like JAK/STAT, PI3K /Akt / mTOR and MAPK leading to activation of NF-kB, which promotes cell proliferation, cell survival, metastasis and angiogenesis. In contrast, Adiponectin activates AMPK pathway and their by inhibiting mTOR pathway.
Role of Leptin in Type-II EMC:

Leptin was first isolated by Jeffrey Friedman, in the year 1994. It is of 167 amino acids long and 16-kDa in weight. Apart from adipose tissue, Leptin is also secreted from placenta, stomach, ovaries, bone marrow and mammary epithelial cells [5, 58–61]. It’s synthesis is influenced by TNF-α, sex hormones and prostaglandins [62]. Leptin binds to a receptors encoded by db gene, which is of six isoforms (ObRa - ObRf) belonging to family of cytokine receptors [63]. In this ObRb receptor is a single transmembrane protein to which Leptin binds and it is expressed throughout the central nervous system (CNS) [64]. Leptin is reported to increase the risk of EMC and ovarian cancer in post-menopausal obese patients [59,60,62,65,66]. It is also reported to activate signalling pathways like Janus kinases/Signal transducer and activator of transcription proteins (JAK/STAT), MAPK, P13K, AMPK and Insulin receptor substrate-1 (IRS) which leads to cell proliferation and survival (Figure-3) [63, 66]. In addition, it also activates aromatase and therefore, promote hormone dependent neoplasms, such as endometrial and breast cancers (Figure-3) [67, 68]. The elevated levels of Leptin in Type-II EMC was further established by the meta analysis study carried out by Wang et al., in the year 2014 [65].These above scientific reports, therefore can strongly implicate the role of Leptin in the Type-II EMC.
Figure-3: Role of Leptin in Type-II EMC:

Leptin binds to Ob-R receptor and initiates signal transduction JAK/STAT, and MAPK pathways. This downstream signalling in-turn activates NF-Kβ leading to cell growth and survival.

Role of Resistin in Type-II EMC:

Resistin was reported for the first time by Steppan et al., in the year 2001 [69]. Resistin is reported to signal through Toll-like receptor 4 (TLR4) receptor, and subsequent activation of P13K/Akt and of NF-Kβ signalling cascades (Figure-4) [47, 67, 70]. Activation of these pathways can cause a spiralling cascade of the cytokines that continually upregulate inflammatory responses and maintain an increased inflammatory state that can further lead to a carcinogenic state [70]. The downstream pro-inflammatory cytokines formed activate JAK/STAT and Microtubule Associated Protein Kinase (MAPK) pathways involved in cell
proliferation, differentiation and metastasis (Figure-4) [71]. NF-κβ activation also leads to upregulation of Intracellular Adhesion Molecule-1 (ICAM) and Vascular Cell Adhesion Molecule-1 (VCAM-1), a group of inflammatory cytokines [72]. These adhesion molecules are responsible for the attachment of metastasized cancers cells on to endometrium, there by leads to development and progression of Type-II EMC [73, 74]. Resistin is also reported to upregulate Stroma Cell Derivative Factor 1 (SDF1) which is reported to promote tumor growth and metastasis (Figure-4) [75]. Hlavan et al., in the year 2011 have reported that Type-II EMC patients shows an higher levels of Resistin in serum [76]. The above fact, therefore, further established the role of Resistin in Type-II EMC.

Figure-4: Role of Resistin in Type-II EMC:

Elevation of Resistin levels lead to activation of TLR4 receptor causing initiation of p38 and PI3K pathways. These in turn lead to phosphorylation of NF-κβ, increasing inflammation, adhesion molecules and Stroma Cell Derived Factor-1 (SDF-1). These inturn leads to increase in reactive oxygen species (ROS) and metastasis, promoting cancer.
Role of Visfatin in Type-II EMC:

Visfatin also known as Nicotinamide phosphoribosyl transferase (Nampt) was first reported by Preiss in 1957, however it was later identified and characterised by Samal et al., in the year 1994 as Pre-B-Cell Colony-Enhancing Factor (PBEF) is mainly secreted by visceral adipose tissue [77, 78]. A recent study shown that the expression of Visfatin is also high in macrophages that infiltrate the adipose tissue [79]. Visfatin acts as cytokine which promotes the expression of various pro-inflammatory cytokines like TNF-α, IL-1B and IL-6 promotes the differentiation of B-cells. Therefore the role of Visfatin can be linked to several inflammatory diseases and also cancer. Visfatin is involved in growth apoptosis and angiogenesis in several mammalian cells [80]. It is also reported to be involved in Nicotinamide adenine dinucleotide (NAD) pathway and has insulin mimetic effects [79, 81, 82]. These diverse roles of Visfatin suggest that it plays an important role in several disease conditions including cancers like breast, colorectal, prostate and gastric cancers [83]. Elevated insulin levels directly stimulate proliferation of endometrial cells by activating mitogenic and anti-apoptotic signalling systems. Visfatin through its insulin mimetic properties was reported to produce similar effects [83, 84]. The second mechanism by which Visfatin increases Type-II EMC risk is by increasing the expression of Stromal SDF-1 via pathways involving MAPK, Extracellular Receptor Kinase (ERK), and integrin B1 resulting in metastasis (Figure-5) [59]. Visfatin also activates IL-6, which further leads to increased expression of STAT3, Nampt pathways thereby increasing the expression of silent mating type information regulation 2 homolog (Sirt) which leads to angiogenesis and cancer cell survival (Figure-5) [85, 86]. Visfatin through several unknown pathways decreases in ROS levels which leads to increased cell protection and there by promoting cancer cell growth (Figure-5) [87]. Studies by Ploska et al., in the year 2018 suggested Visfatin as a good marker for Type-II EMC and reported that high levels of serum Visfatin predicts poor
prognosis in Type-II EMC patients [88]. In a similar study by Nergiz et al., in the year 2015, higher serum Visfatin levels were reported in Type-II EMC patients than healthy individuals [89]. From these data Visfatin can be considered an important risk factor in Type-II EMC.

Excessive Visfatin levels activates IL-6, β1 integrin receptors which phosphorylates MAPK/ERK and JAK/STAT. This in turn leads to increase in Cell survival and migration via Sirt-1/Sirt-6 and SDF-1. Visfatin through unknown pathways, degrades the ROS shielding the cell from cellular damage.

**Figure-5: Role of Visfatin in Type-II EMC:**

1. Excessive Visfatin levels activates IL-6, β1 integrin receptors which phosphorylates MAPK/ERK and JAK/STAT. This in turn leads to increase in Cell survival and migration via Sirt-1/Sirt-6 and SDF-1. Visfatin through unknown pathways, degrades the ROS shielding the cell from cellular damage.
Role of Adiponectin in Type-II EMC:

Adiponectin is secreted from the adipose tissue and is the only adipokine with an inverse relationship to fat mass [5, 90]. Adiponectin is encoded by the gene AdipoQ, which is made up of 244 amino acids and is 30kDa in weight. Adiponectin was discovered in the mid-1990s as a requirement for adipocyte differentiation of 3T3-L1 cells [90–92]. A part of its role in the regulation of adipocyte differentiation, in vitro studies revealed that Adiponectin can prevent the proliferation of various cancer-derived cell types such as breast cancer, endometrial cancer, prostate cancer and colorectal cancer [43, 91, 92]. It binds to receptors like AdipoR1 and AdipoR2 and inhibits proliferation and metastasis via activation of AMPK pathway which inturns inhibits mTOR pathway (Figure-6) [92–95]. Reduction in levels of Adiponectin causes increase cell proliferation and metastasis in the endometrium [48]. Decreased Adiponectin receptor expression is associated with a histological higher grade of endometrial cancer [96]. Hence, Adiponectin receptor expression decrease is a proposed contributor to cancer progression and can be a target of treatment for endometriosis adenocarcinomas (Figure-6) [93]. The elevated levels of Adiponectin in Type-II EMC was further established by the meta analysis study carried out by Zengf et al., in the year 2015 [97]. From their studies, it was demonstrated that increased serum Adiponectin will reduce the risk of Type-II EMC development in Postmenopausal women.
Adiponectin binds to AdipoR1/AdipoR2 receptor which initiates the signalling of AMP-activated protein kinase (AMPK) which inhibits mTOR pathway, leading to decreased cell proliferation.

Possible Role of Adipokine Modulators in the Treatment of Type-II EMC:

Various studies have demonstrated the role of adipokines especially Adiponectin, Leptin, Visfatin and Resistin in the pathogenesis of Type-II EMC. There are many drugs which are used for the treatment of various conditions have been reported to act by modulating adipokines levels. Some of these agents include Omega-3-fatty acids (Hexadecatrienoic acid, Eicosatrienoic acid), Statins (Atorvastatin, pravastatin), Fibrates (Gemfibrate, Benzfibrate, fenfibrate), Thiazolidinediones (TZD) (Rosiglitazone, Pioglitazone) etc., TZD are reported to increases Adiponectin level and decreases Leptin, Visfatin and Resistin levels through modulating the gene expression of these proteins [98–100] . Niacin is reported to increase Adiponectin and has no effect/least effect on Visfatin, Leptin and Resistin by modulating GPR109A receptor [101]. However, Anti-hyperlipidemic drugs like statins and fibrates decrease the accumulation of adipose tissue leading to increased adiponectin and decreased
leptin and Visfatin [100, 102]. Omega-3-fatty acids are reported to decrease the leptin levels and little effect on TNF-\(\alpha\) level and increase adiponectin levels by activation of PPAR-\(\gamma\) gene [103]. The above adipokine modulators increase adipokine like adiponectin and decrease adipokines such as Visfatin, Leptin and Resistin. Adiponectin is reported to prevent Type-II EMC, whereas, Visfatin, Leptin and Resistin are reported to promote Type-II EMC (Table-1). The above adipokine modulators therefore may have possible beneficial effects in the treatment of Type-II EMC.

### Table-1 Effect of different adipokine modulators on circulating levels of adipokines

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Adipokine modulators</th>
<th>Drugs</th>
<th>Effects on circulating adipokines</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thiazolidinediones (TZD)</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td>2</td>
<td>Statins</td>
<td>Atorvastatin, Pravastatin</td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td>3</td>
<td>Fibrates</td>
<td>Gemfibrate, Benzfibrate, Fenfibrate</td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td>4</td>
<td>Omega-3-fatty acids</td>
<td>Hexadecatrienoic acid, Eicosatrienoic acid</td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td>5</td>
<td>Niacin</td>
<td>Niacor, Niaspan</td>
<td>Increases</td>
<td>Increases (or) no effect</td>
</tr>
</tbody>
</table>

**Conclusion:** The Adipokines seems to play an important role in the pathogenesis of Type-II EMC. The drugs which act by modulating adipokines may therefore, plays an important role in the treatment of Type-II EMC. However, further research needs to be conducted to establish their claims.
Compliance with Ethical Standards

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Conflict of Interest: The first author Garikapati Kusuma Kumari declares that she has no conflict of interest. The second author A.V.V.V.Ravi Kiran declares that he has no conflict of interest. The third author and corresponding author Dr. Praveen T.K declares that he has no conflict of interest. The fourth author Pavan Kumar Chintamaneni declares that he has no conflict of interest. The fifth author Sai Kiran S.S. Pindiprolu declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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