Possible Role of Thiazolidinedione in the Management of Type-II Endometrial cancer

G. Kusuma Kumari; Praveen T. Krishnamurthy; A.V.V.V.Ravi Kiran; Pavan Kumar Chintamaneni; Sai kiran S.S Pindiprolu

Department of Pharmacology, JSS College of Pharmacy (a constituent college of JSS Academy of Higher Education and Research) Udhagamandalam, Tamil Nadu 643001, India.

Corresponding author:
Praveen T. Krishnamurthy
Professor & Head
Department of Pharmacology
JSS College of Pharmacy, Ooty
e-mail: praveentk7812@gmail.com
Possible Role of Thiazolidinedione in the Management of Type-II Endometrial cancer

Abstract:

Type-II Endometrial Cancer is one of the most common types of gynaecological cancer worldwide, affecting more than 2.7 million people. Clinical evidence shows that adipokine levels are abnormally altered in Type-II EMC and reported to be responsible for uncontrolled proliferation and metastasis. Reversing the altered adipokine levels, therefore, help to control the proliferation and metastasis. In the present review we focus on the possible role of Thiazolidinediones in positive alterations of adipokine levels to benefit in the management of Type-II Endometrial Cancer.

Keywords: Type-II Endometrial Cancer, Thiazolidinediones, Adipokines, Adiponectin, Leptin, Resistin, Visfatin.
INTRODUCTION

Endometrial cancer (EMC) is most common gynaecological cancer in women, affecting about 2.7 million people worldwide [1]. Unlike Type-I EMC which is estrogen dependent, Type-II EMC is estrogen independent. Obesity is considered as one of the major risk factor and adipokines are reported to play an important role in the pathogenesis [2].

Adipokines are endogenous adipocyte secretions which are comprised of Adiponectin, Leptin, Visfatin, Resistin and others. Adiponectin, also known as Adipocyte complement-related protein 30kDa (Acpr30), which is mainly produced in white adipose tissue (WAT) [3]. Downstream signalling of Adiponectin receptors, mediate cell proliferation and apoptosis by various pathways such as AMP-activated protein kinase (AMPK), Peroxisome Proliferator Activated Receptors-γ (PPAR-γ), Extracellular signal-regulated kinases (ERK), and Protein Kinase B (Akt) [3–6].

Leptin, an adipokine, secreted mainly by WAT, reported to play an important role in energy homeostasis and cell proliferation. It is found to promote cell proliferation by activating pathways like JAK/STAT3, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/ protein kinase B (PI3K/Akt). Resistin, is a cysteine rich protein, belonging to ‘Resistin-like molecules’ family. It is secreted by immune cells (monocytes and macrophages), ovary and endometrium [7,8]. It is reported to bind to Toll-like
receptor 4 (TLR4) and initiate NF-kβ pathway resulting in increased cell proliferation and tumor invasion [9–13]. Visfatin, also known as pre-B-cell colony-enhancing factor, reported to be overexpressed in colon, stomach, brain, endometrium and breast cancer [14–17].

Peroxisome Proliferator Activated Receptors (PPARs-α, β, γ, δ) are Type II nonsteroidal nuclear receptors which heterodimerize with the retinoid X receptor (RXR) and bind to peroxisome proliferator’s response elements (PPRE) and regulate transcription of various genes [18]. These transcription factors have a diverse range of physiological functions like energy homeostasis, cell differentiation, proliferation and apoptosis. Out of the 3 isoforms, PPAR-γ is most targeted nuclear receptor. It is found predominantly expressed in adipocytes where it control adipokine gene expression to regulates adipocyte differentiation and energy homeostasis. In addition to adipocytes, PPAR-γ is also overexpressed in many tumors like breast, endometrial, and thyroid where it regulates the proliferation, differentiation and apoptosis of cell [18–22].

PPAR-γ activation by various endogenous and exogenous ligands lead to differential regulation of adipokine genes such as increased Adiponectin gene expression and decreased Leptin, Resistin, IL-6, TNF-α and Omentin gene expression [23]. Thiazolidinedione’s (TZD’s) or Glitazones are exogenous ligands of PPAR-γ and reported to modulate PPAR-γ mediated adipokine gene expression[24–26].
Hypothesis:

In Type-II EMC Leptin, Resistin are overexpressed whereas Adiponectin in under-expressed. The above changes in the adipokine levels are responsible for the uncontrolled proliferation and metastasis of Type-II EMC. One of the strategies is to regulate uncontrolled proliferation of Type-II EMC by regulating the gene expression of adipokines. TZD’s are well known for their ability to differentially regulate the gene expression of various adipokines through PPAR-\(\gamma\) activation. We, therefore, hypothesize that TZD’s may have beneficial effect in Type-II EMC by reversing the abnormal gene expression of adipokines (Figure-1).

Justification of hypothesis:

Many researchers have reported that adipokines like Adiponectin, Leptin, Visfatin etc., play a crucial role in Type-II EMC [27–30]. A study by Patricia et al., in the year 2013, showed that a correlation exist between the Type-II EMC and both Leptin (Positive correlation) and Adiponectin (Negative correlation) [31]. Similarly, a study by Yunusova et al., in the year 2015, reported that decreased Adiponectin and increased Leptin levels were observed in more than 60 patients suffering with Type-II EMC, and they have concluded that alterations in there adipokines may be responsible for increased tumor proliferation and invasion in Type-II EMC [32]. Another study by Zeng et al., in
the year 2015, concluded that high serum Adiponectin levels will reduce the risk of Type-II EMC in group of postmenopausal women [33].

Many studies have revealed that TZD’s have adipokine modulatory activity mainly by altering Adiponectin and Leptin levels [15,18,19,21,34–37]. A study by Sharabi et al., in the year 2017, demonstrated that PPAR-γ agonist’s action on hypoadiponectinemia rats. Their results showed that PPAR-γ agonists increased gene expression and plasma levels of Adiponectin [34]. Similarly, a study by Maeda et al., in the year 2007, demonstrated that PPAR-γ ligands effects on expression of Adiponectin levels. Their results showed that TZD’s treated groups expressed higher Adiponectin concentrations and lowered the TNF-α concentrations [35]. Another study by Quinn et al. in the year 2003, reported that activation of PPAR-γ by TZD’s showed elevation in Adiponectin levels but substantial decrease in Leptin, TNF-α, PAI and IL-6 levels [38]. Sun et al., in the year 2006, demonstrated that Rosiglitazone elevated the Adiponectin levels by improving the expression of Adiponectin receptors in liver[39]. Kallen et al., in the year 1996, had reported that TZD’s inhibited the expression of Leptin in adipose tissue [40]. From the above studies, it is clear that use of TZD’s may increase Adiponectin and decrease Leptin, Resistin, IL-6, TNF-α, Omentin, Plasminogen activated Inhibitor (PAI) and other adipokines [Monocyte chemotactic protein-1(MCP-1), Retinol binding protein -4 (RBP-4) and vaspin], in adipose tissue (Table-1).
**Table-1:** Effect of TZD’s on adipokines

<table>
<thead>
<tr>
<th>ADIPOKINES</th>
<th>EFFECT OF TZD’S</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>↑</td>
<td>[3,30,35–43]</td>
</tr>
<tr>
<td>Leptin</td>
<td>↓</td>
<td>[40,47,48]</td>
</tr>
<tr>
<td>Visfatin</td>
<td>X</td>
<td>[49]</td>
</tr>
<tr>
<td>Resistin</td>
<td>~less effect/ X</td>
<td>[47]</td>
</tr>
<tr>
<td>TNF-α</td>
<td>↓</td>
<td>[23,25,26,38]</td>
</tr>
<tr>
<td>PAI</td>
<td>↓</td>
<td>[38]</td>
</tr>
<tr>
<td>IL-6</td>
<td>↓</td>
<td>[18,25,26,38]</td>
</tr>
<tr>
<td>Other adipokines</td>
<td>??</td>
<td>[24,26,42]</td>
</tr>
<tr>
<td>(MCP-1, RBP-4,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaspin, omentin, chimerin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TNF-α : Tumor Necrosis Factor-α; PAI: Plasminogen Activator Inhibitor I; IL-6 : Interleukin 6; TZD’s : Thiazolidinediones; Other adipokines: Omentin, Apelin, Chimerin, Vaspin, Monocyte chemotactic protein-1(MCP-1), Retinol binding protein -4 (RBP-4). ↑- Increased, ↓- Decreased, X- not effected, ??- Unknown actions
Various factors like increased obesity, postmenopausal condition and mutations in genes lead to release of various adipokines like Adiponectin, Leptin, Visfatin etc. from adipose tissue in Type-II EMC. These adipokines initiate the AMPK, MAPK, JAK/STAT3 and mTOR pathways. Of these Adiponectin activated-AMPK inhibits the mTOR pathway leading to decreased cell proliferation. The remaining adipokine mediated pathways will in turn phosphorylate the NF-κβ which promotes cell proliferation and tumor formation. Peroxisome proliferator activated receptors gamma (PPAR-γ) agonists like TZD’s initiate the transcription, leading to increase in levels of Adiponectin decreases the expression of Leptin, Resistin, Visfatin, TNF-α, IL-6 and results in unwanted proliferation, angiogenesis and induces apoptosis.
**Conclusion:**

Adipokines are reported to play an important role in the pathogenesis of Type-II EMC. One of the strategies to control the cell proliferation is to regulate the gene expression of these hormones. TZD’s are one of the potential drug molecules having proven ability to regulate adipokine gene expression. The above potentials of TZD’s therefore, may help to regulate uncontrolled cell proliferation and metastasis in Type-II EMC.

**Reference**


Regulatory, Integrative and Comparative Physiology 2005;289:R486–94.


[34] Sharabi Y, Oronherman M, Kamari Y, Avni I, Peleg E, Shabtay Z, et al. Effect of PPAR-γ Agonist on Adiponectin Levels in the Metabolic Syndrome:


