

Possible role of Thiazolidinedione in the management of Type-II Endometrial Cancer



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ABSTRACT

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

Introduction

Endometrial cancer (EMC) is most common type of 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].

Adipocytokines are endogenous adipocyte secretions which are comprised of Adiponectin, Leptin, Visfatin, Resistin and others. Adiponectin, also known as Adipocyte complement-related protein 30 kDa (Acpr30), which is mainly produced in white adipose tissue (WAT) [3]. Downstream signalling of Adiponectin receptors, mediate cell proliferation and apoptosis by activating 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, 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 predominantly 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- κ B

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, especially as a target for the treatment of Type-2 diabetes mellitus. 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].

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Hypothesis

In Type-II EMC adipokines such as Leptin, Resistin, Visfatin are overexpressed whereas Adiponectin is under-expressed. The above changes in the adipokine levels are reported to be responsible for the

uncontrolled proliferation and metastasis of Type-II EMC. One of the treatment strategies, therefore is to regulate uncontrolled proliferation of Type-II EMC by modulating the gene expression of adipokines. TZD's are well known for their ability to differentially regulate the gene expression of various adipokines through PPAR- γ activation. We,

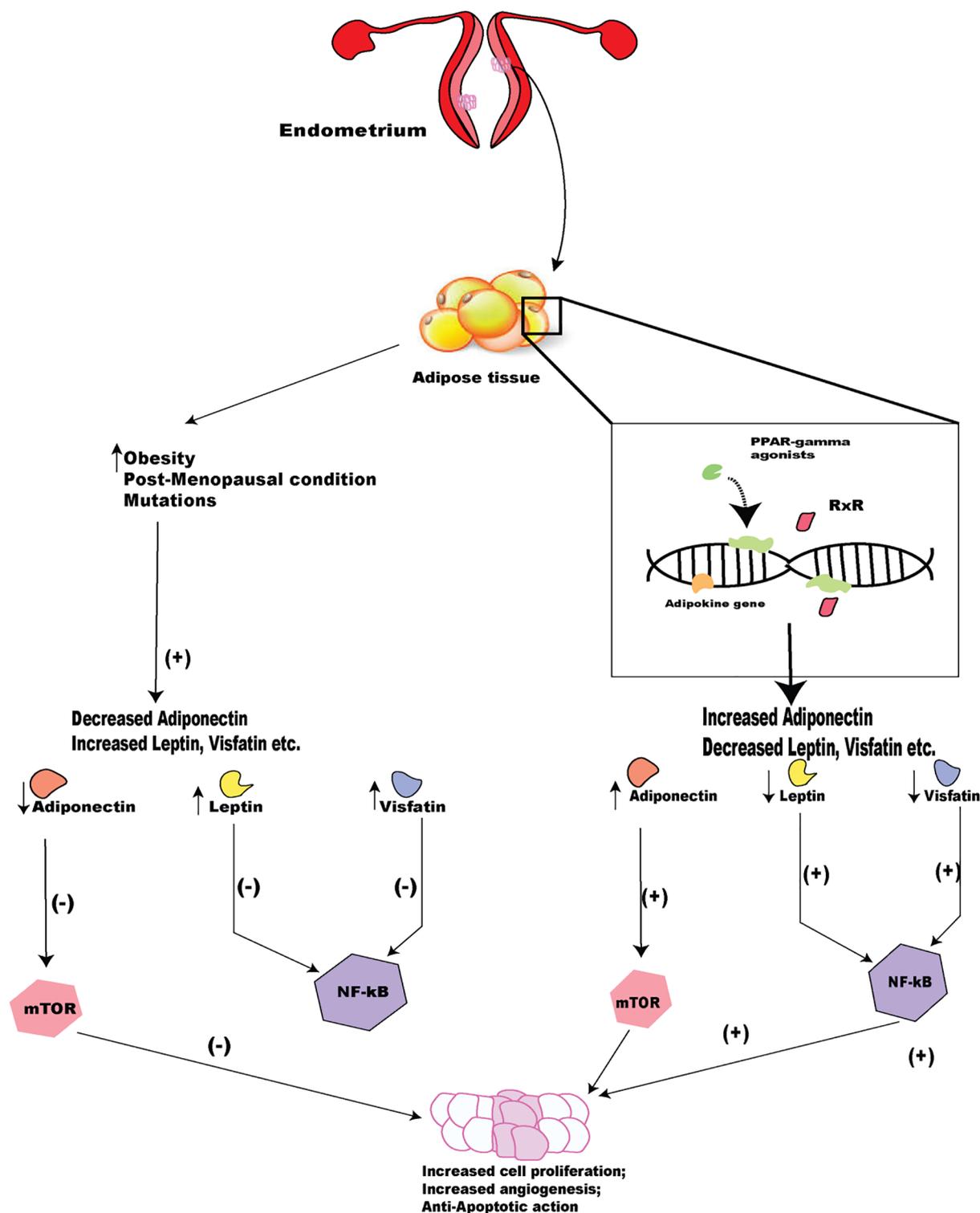


Fig. 1. Actions of TZD's on PPAR- γ in Type-II EMC: Various factors like increased obesity, postmenopausal condition and mutations in genes lead to release of various adipokines like Adiponectin, Leptin, Visfatin etc. from adipose tissue in Type-II EMC. These adipokines initiate the AMPK, MAPK, JAK/STAT3 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-k β 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 promotes apoptosis.

Table 1
Effect of TZD's on adipokines.

Adipokines	Effect of TZD'S	Reference
Adiponectin	↑	[3,30,35–43]
Leptin	↓	[39,46,47]
Visfatin	X	[48]
Resistin	~less effect/ X	[47]
TNF-α	↓	[23,25,26]
IL-6	↓	[18,25,26]
Other adipokines (MCP-1,RBP-4, Vaspin, omentin, chimerin)	??	[24,26,41]

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.

therefore, hypothesize that TZD's may have beneficial effect in the management of Type-II EMC by reversing the abnormal levels of adipokines (Fig. 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 Type-II EMC and the serum levels of Leptin (Positive correlation) and Adiponectin (Negative correlation) [31]. Similarly, a study by Yunusova *et al.*, in the year 2015, reported that the decreased Adiponectin and increased Leptin levels were observed in more than 60 patients suffering with Type-II EMC and they conclude that the alterations 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 [15,18,19,21,34–37,44,45]. A study by Sharabi *et al.*, in the year 2017, demonstrated that administration of the PPAR-γ agonist's in high fructose fed rats reversed hypo adiponectinemia by increasing gene expression of Adiponectin [34]. Similarly, a study by Maeda *et al.*, in the year 2007, demonstrated that administration of PPAR-γ agonists such as TZDs in obese mice has increased the expression of Adiponectin and lowered the TNF-α levels in serum [35]. Sun *et al.*, in the year 2006, demonstrated that Rosiglitazone elevated the mRNA and protein levels of Adiponectin receptors in hepatocytes (HepG2) and in mice liver [38]. Kallen *et al.*, in the year 1996, had reported that TZD's inhibited the expression of Leptin in adipose tissue [39]. 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).

It would be much more appropriate if the beneficial role of TZD's can be established in *in vitro* and *in vivo* (preclinical & clinical) models of Type-II EMC. In *in vitro*, TZD's beneficial effects should be evaluated against various Type-II EMC cell lines such as, HEC-1B, HEC-1A, HEC-50co, KLE and Ishikawa cell lines [49]. In addition, *in vivo* benefits should be assessed in preclinical Type-II EMC models such as, xenograft nude mice models [50]. Finally the benefits of TZD's should be established by conducting randomized controlled clinical studies in patients suffering with Type-II EMC.

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.

Conflict of interest

None.

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