

## Estimation Arginase Activity in the Serum of Uterine Fibroid Females and its Relationship with Other Parameters

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### Abstract

The research includes a clinical study of Arginase and its relation with uterine fibroid. The normal value of arginase activity in female serum was found to be  $(0.52 \pm 0.02$  IU/L) in healthy group at age (35-55) years. The study also showed a highly significant increase in arginase activity ( $7.99 \pm 0.23$  IU/L) in serum of uterine fibroid patients group at (35-55years) in comparison to healthy. The results also indicated a highly significant increase in the level of progesterone, estradiol, prolactin, peroxy nitrite and malondialdehyde in patients group. While a highly significant decrease in concentration of adiponectin in patients group was found in comparison to healthy.

**Keywords:** Arg, Adipo Q, PRO, E<sub>2</sub>, PRL, Peroxynitrite, MDA.

**Abbreviations:** Arg, Arginase; Adipo Q, Adiponectin; PRO, Progesterone; E<sub>2</sub>, Estradiol; PRL, Prolactin; MDA, Malondialdehyde.

### Introduction

Uterine fibroids are benign (not cancer) tumors<sup>(1)</sup> growths that develop from the muscle tissue of the uterus<sup>(2)</sup>. They also are called leiomyomas, myomas, fibromyomas, leiomyofibromas. Because the tumor consists of uterine smooth tissue as well as fibroids tissue, the term fibroid does not adequately capture the name of the lesion<sup>(3)</sup>. These tumors have prevalence ranging from 20% to 40% of the women depending on the age<sup>(4)</sup>. Uterine fibroids can cause severe problems for women and most of the uterine fibroids do not cause symptoms<sup>(5)</sup>. The size, shape and location of fibroid vary greatly<sup>(6)</sup>. They may be present inside the uterus, on its outer surface or within its wall, or attached to it by a stem<sup>(7)</sup>.

The aim of this study were to determine arginase activity in serum of females with uterine fibroid and its relationship with adiponectin, progesterone, estradiol, prolactin, peroxy nitrite and malonaldehyde.

The causes of the uterine fibroids may be attributed to the genetic change<sup>(8)</sup>. hormones (estrogen and progesterone)<sup>(9)</sup> and other growth factors such as insulin-like growth factor<sup>(10)</sup>.

Arginase belongs to the urea hydrolase family of enzyme. The arginase (EC. 3.5. 3.1), catalyzes the fifth and final step in the urea cycle, a series of biochemical reactions in mammals during which the body disposes of harmful ammonia. Specifically, arginase-convert L-arginase into L-ornithine and urea<sup>(11)</sup>.

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and oxidation<sup>(12)</sup>. Therefore, adiponectin has multiple functions including anti oxidation and antiinflammation potential<sup>(13)</sup>. Indeed, some investigators have indicated that low circulating adiponectin levels may be associated with pathogenesis of liver cancer, adiponectin is abundantly expressed and secreted by adipose tissue, and circulates as different multimer complexes<sup>(14)</sup>. Multimer complex formation of adiponectin, as a major biological functions of this adipocytokine<sup>(15)</sup>.

Oxidative stress can be identified as an imbalance between the oxidant materials (free radical and their metabolism outputs) and antioxidants. The cells contain oxidant materials more than antioxidants, which is lead to destroy the big vital molecules of the body. Oxidative stress happens when the level of oxidant compounds exceed the ability of antioxidants on removing it<sup>(16)</sup>.

### Materials and Methods

#### Subjects

In this study were collected during the period from 1<sup>st</sup> Dec. 2013 until the end of May 2014 at obstetrics and gynecology department of two hospitals in Baghdad city (Baghdad teaching hospital and Al-Yarmuk teaching hospital). The females included two groups, patients and healthy. The patients group consisted of (50) females with uterine fibroids were diagnosed by ultrasound. The healthy group consisted of (30) females as control, two groups aged (30-55) years.

#### Specimens collection and analysis

Venous blood samples were drawn from each patient then transferred immediately to a clean dry plain tube. After removing the needle, the blood was allowed to clot for at least (10-15) min, at room temperature and then centrifuged for (15) min, at (3500 rpm). Serum is removed and assayed immediately and store the samples at 4°C for the purpose of conducting the required measurements.

#### Methods

Arginase activity was measured in serum according to (Coulombe., 1963)<sup>(17)</sup>. Serum adiponectin, progesterone, estradiol and prolactin levels were measured using an enzyme- linked immunosorbent assay. Peroxynitrite (ONOO<sup>-</sup>) was measured by the modified method described by (Vanuffelenet *al.*, 1998)<sup>(18)</sup> based on the ability of peroxynitrite to convert the phenol to nitrophenol which can be estimated spectrophotometrically. Serum MDA was measured by a modified method described by (Schmede and Holmer.,1989)<sup>(19)</sup> using thiobarbituric acid.

## Results

The results of the measured biochemical parameters are summarized in the table (1). The result showed a significant increase ( $p < 0.000$ ) in level of arginase, progesterone, estradiol, prolactin, peroxynitrite and MDA in serum of uterine fibroid females compared to healthy females. There was a significant decrease ( $p < 0.000$ ) in adiponectin levels in sera females with uterine fibroid compared to healthy ones.

**Table (1): Values of biochemical parameters in females of uterine fibroid and healthy females.**

Biochemical parameters	Healthy females (n=30)	Uterine fibroid females (n=50)
	Mean $\pm$ SE	Mean $\pm$ SE
Arginase (IU/L)	0.52 $\pm$ 0.02	7.99 $\pm$ 0.23*
Adiponectin (ng/mL)	16.93 $\pm$ 0.29	13.22 $\pm$ 0.12*
Progesterone (ng/mL)	0.95 $\pm$ 0.05	2.07 $\pm$ 0.06*
Estradiol (pg/mL)	107.39 $\pm$ 3.93	265.42 $\pm$ 6.37*
Prolactin (ng/mL)	8.57 $\pm$ 0.21	17.13 $\pm$ 0.38*
Peroxynitrite( $\mu$ mol/L)	45.16 $\pm$ 0.86	83.29 $\pm$ 0.4*
MDA (mmol/L)	0.67 $\pm$ 0.04	3.01 $\pm$ 0.07*

\*Significant differences at ( $p < 0.0001$ )

## Discussion

Arginase can redirect the metabolism of L-arginine in smooth muscle cells from nitric oxide (NO) to L-ornithine and the formation of polyamines and L-proline, which can induce vascular lesion formation by stimulating smooth muscle cell proliferation and collagen deposition. These action of arginase are further magnified by the suppression of NO release, which serves as a well recognized inhibitor of smooth muscle cell growth and collagen synthesis<sup>(20)</sup>.

While (Kaplan *et al.*, 2012)<sup>(21)</sup>, referred to that increased arginase activity may limit nitric oxide synthase (NOS) activity and lead to a weakening of the inhibitor effect on xanthine oxidase activity. In this case, it result in more superoxide radical production and tissue damage.

As evidenced by the up regulation of arginase in specific disease states, its distribution in vagina and its modulation by sex steroid hormones, this enzyme may also tissue growth fibrosis, and immune function<sup>(22)</sup>. On other hand, the reason of high arginase activity may be attributed to change in permeability of fibroid cell as a result of many biochemical changes in cell surface, that is included changes in appearance of cell surface such as variation in glycolipid and mucine. Like in this alter leads to excrete several of enzymes from cells to serum and one of these enzymes is arginase<sup>(23)</sup>.

The present study found a significantly decrease ( $p < 0.000$ ) of serum adiponectin levels in uterine fibroids females than levels of healthy group. The results are agreement with (Chen *et al.*, 2004)<sup>(24)</sup> results, in which it was found a significant decrease in adiponectin level. The repression of adiponectin on leiomyoma cell proliferation in the rat may explain a crucial role of adiponectin in the association of metabolic syndrome with uterine leiomyoma<sup>(25)</sup>. Serum adiponectin levels are decreased in women with uterine leiomyomas and play a possible role in the pathogenesis of leiomyomas, through insulin-or estrogen-related pathways<sup>(24)</sup>. Adiponectin plays an important role in regulation several metabolic pathways, involving glucose and fatty acid catabolism; low levels of the hormone have been implicated in the development of metabolic syndrome and type 2 diabetes, which are condition also associated with a higher risk of fibroid development. It has been found that adiponectin inhibits rats uterine leiomyoma cell growth in a dose- dependent fashion. Thus, pathways associated with adiponectin could possibly serve as therapeutic targets against fibroid development in the future<sup>(1)</sup>. Adiponectin plays an important role in human reproduction system and fertility of women. Adiponectin concentration decreases in women with endometriosis and endometrial cancer<sup>(26)</sup>. Both (Rasulet *al.*, 2011 and Koncsoset *al.*, 2010)<sup>(27,28)</sup>. Were pointed at the low level of adiponectin become macrophages in adipose tissue more efficiently and produce large amount of inflammatory cytokines and it is adiponectin anti- inflammatory. During our reading for similar studies, we found that because it's role as anti-proliferation for leiomyoma cells, adiponectin level was expected to be decreased in sera of females with uterine fibroids (The relationship between adiponectin and fibroids is reverse).

The results in table (1) showed a highly significant increase ( $p < 0.000$ ) of serum progesterone levels in

uterine fibroid patients than levels of healthy group. The results are agreement with other investigators (Englurdet *et al.*, 1998; Nisolle *et al.*, 1999)<sup>(29,30)</sup>. Which showed uterine fibroid have increased concentration of progesterone receptors A and B compared with normal myometrium. The highest mitotic counts are found during the secretory phase at peak of progesterone production, and mitotic counts are higher in women treat with medroxy progesterone acetate (MPA) than in untreated controls (Kawaguchi *et al.*, 1991)<sup>(31)</sup>. Gonadotropin releasing hormone (GnRH) agonists decrease the size of uterine fibroids, but progestin given concurrently with GnRH prevents a decrease in size<sup>(32)</sup>.

Table (1) showed a highly significant increase in estradiol level in serum of uterine fibroid females ( $p < 0.000$ ) when compared with healthy females. The obtained results were in agreement with those reported by other (Mac Mahon *et al.*, 1982; Apter *et al.*, 1989; Moor *et al.*, 1991)<sup>(33-35)</sup>. Which showed a levels of estradiol within uterine fibroid are higher than in normal myometrium. Consistent with idea, uterine fibroid show a higher proliferative index than normal myometrium through the menstrual cycle. (Cook & Walker, 2004)<sup>(36)</sup>. The patients who had higher levels of estradiol also had earlier menarche than the controls. Likewise, estradiol levels have been observed to be higher among nulliparous women than among parous women (Bernstinet *et al.*, 1991)<sup>(37)</sup> and to increase with age (up to 40 years) during the mid-cycle and luteal menstrual phase among nulliparous women but to decline with age among parous women. (Dorgan *et al.*, 1995)<sup>(38)</sup>.

The statistical analysis showed that there is a highly significant increase in prolactin level serum of uterine fibroid females ( $p < 0.000$ ) when compared with the healthy females. This finding is in agreement with (Mitchell *et al.*, 1989)<sup>(39)</sup>. Which showed that, the level of prolactin is higher in uterine fibroid patients. Leiomyoma has the ability to synthesize prolactin which increase the evidence that cells of mesenchymal origin that arise near the paramesonephric ducts have a latent ability to express the genome for prolactin synthesis in leiomyoma *in vivo* suggest that this potential genome expression is activated either in smooth muscle cells or stromal cells during the transformation of normal cell to leiomyoma cells (Daly *et al.*, 1984)<sup>(40)</sup>.

The increase in the levels of the free radicals nitric oxide ( $\text{NO}\cdot$ ) and super oxide ( $\text{O}_2\cdot^-$ ) produced  $\text{ONOO}^-$  may be occur in uterine fibroid. The results in table (1) showed a highly significant elevation in peroxynitrite in the serum of uterine fibroid females compared with healthy females. The increase of peroxynitrite might be due to excess of  $\text{O}_2\cdot^-$  which is formed as a result of reaction between  $\text{NO}\cdot$  and  $\text{O}_2\cdot^-$ . (Paul *et al.*, 1998)<sup>(41)</sup>.

Table (1) showed that there is a highly significant increase in MDA concentration in serum of uterine fibroid females ( $p < 0.000$ ) when compared with the healthy females. These result were in agreement with other investigations (Pejicet *et al.*, 2009)<sup>(42)</sup>. Which showed an increase in concentration of lipid peroxidation products, as marker of oxidative stress whereas the level of antioxidants decreased in uterine fibroid patients. The rise in MDA concentration could be due to increased generation of (ROS) due to the excessive oxidative damage generation in uterine fibroids patients, oxygen radical production, which increased with clinical progression of diseases involves increased lipid peroxidation, as a result of which there are cellular membrane degeneration and DNA damage (Pejicet *et al.*, 2006)<sup>(43)</sup>. Finally increase in levels of MDA indicated the upsurged lipid peroxidation as a consequence of the increase in free radical generation, the free radical may cause profound alteration in the function of the cell membrane and also structural organization of DNA leading to mutation, therefore, it can be stated that lipid peroxidation product is one of the possible causes of uterine fibroid progression (Bilal, K.M., 2013)<sup>(44)</sup>. Oxidative stress plays a key role in numerous such as chronic inflammatory diseases (Kavianet *et al.*, 2012)<sup>(45)</sup>. In endometriosis, a metastatic benign disease (Borghese *et al.*, 2010)<sup>(46)</sup>, endometriotic cells display an increase in endogenous oxidative stress with ROS produced in excess and failures in ROS detoxification pathways (Leconte *et al.*, 2011)<sup>(47)</sup>. In neoplastic condition, the intracellular redox status controls tumor cell proliferation (Alexandreet *et al.*, 2006)<sup>(48)</sup>, and enhances the metastatic potential of tumor cells (Ishikawa *et al.*, 2008)<sup>(49)</sup>. Estrogen as well as estrogen metabolites have been reported to act as pro-oxidants (Bolton *et al.*, 2002)<sup>(50)</sup>. Estrogen induced ROS play important roles in cell transformation, cell proliferation migration and invasion by increasing genomic instability and influencing redox sensitive transcription factors (Okohet *et al.*, 2011)<sup>(51)</sup>. Several reports have suggested the role of the oxidative stress in the development of uterine leiomyomas in the present study we assayed serum oxidative stress marker in a large of females with uterine leiomyomas (Vurlet *et al.*, 2012)<sup>(52)</sup>.

## Conclusion

These data suggest that arginase activity increased in subjects with uterine fibroid. Decreased in adiponectin levels also recorded in this study, that may resulted from the effect of elevation in lipid peroxidation on the permeability of cell membrane, and the high concentration of the hormones (progesterone, estradiol and prolactin).

The present study suggests that arginase may serve as an indicator uterine fibroid. As our knowledge, no previous studies have showed these results in uterine fibroid.

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