

## SERUM ARGINASE-2 LEVEL IN PATIENTS WITH VASCULOGENIC ERECTILE DYSFUNCTION

By

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### ABSTRACT

**Background:** Erectile dysfunction (ED) has considerable impact on the quality of life of middle-aged men and is a significant global health problem with estimates of 33–52% prevalence. Although the origins of ED were thought to be psychogenic or neuropathic, evidence now clearly suggests that the predominant etiology is vasculogenic.

**Objective:** Evaluation the effect of the level of serum arginase II on erectile function.

**Patients and methods:** The current study was carried out on 80 individuals attending the outpatient clinic of Andrology, Al-Azhar University Hospitals.

Selected individuals were divided into 2 equal groups:

- **Group I:** Individuals with vasculogenic erectile dysfunction.
- **Group II:** Matched healthy individuals as controls.

All patients were subjected to full history taking including personal history, sexual history, past history of medical disorders or operations. Evaluation of erectile function using a bridged five-item version of the International index of erectile function-5 questionnaire (IIEF-5), penile duplex, general and genital examination, and measurement of serum arginase 2 were done.

**Results:** There was a statistically highly significant difference between patients and controls as regard serum arginase 2 (ng/ml). There was marked increase in serum arginase 2 level and prevalence of ED with increased age. There was a significant correlation between serum arginase 2 level and diabetes mellitus with significant difference in serum arginase 2 level between different types of vasculogenic erectile dysfunction. The highest percentage was to corporovenogenic erectile dysfunction (45%), followed by arteriogenic erectile dysfunction (32.5%), and finally mixed type (22.5%). With increase in serum arginase 2, there will be decrease in IIEF-5 score and an increase in erectile dysfunction, and that higher levels of serum arginase 2 level was in patients with severe ED with IIEF-5 score (5-7). There was a statistically negative correlation and significant between serum arginase 2 level and IIEF-5 score.

**Conclusion:** Arginase 2 played an important role of male sexual health as with increase age more endothelial dysfunction.

### INTRODUCTION

Erectile dysfunction (ED) is the persistent inability to attain and/or maintain an

erection sufficient to permit satisfactory sexual performance (Moncada et al., 2014).

Nitric oxide (NO) is one of the most important molecules involved in the physiology of erection, and its bioactivity usually decreases in cardiovascular disease (CVD). While this molecule is produced by three different isoforms of NO synthases, two isoforms (endothelial and neuronal NOS) are considered of paramount importance for normal erectile function (**Lacchini and Tanus-santus, 2014**).

All NOS enzymes utilizes L-Arginine as substrate for NO synthesis. However, this substrate is also used by other enzyme, i.e. arginase 1 and arginase 2 (**Lacchini et al., 2015**).

In most mammals, two isozymes of this enzyme exist: arginase 1 functions in the urea cycle, and located in the cytoplasm of the liver, and arginase 2 has been implicated in the regulation of the arginine/ornithine concentrations in the cell. It is located in mitochondria of several tissues, with most abundance in the kidney, prostate and vasculature. It may be found at lower levels in macrophages, lactating mammary glands, and brain (**Di Costanzo et al., 2007**).

Arginase activity has been detected in a number of non-hepatic tissues that lack a complete urea cycle. Mitochondrial arginase 2 necessitates production of ornithine, proline, and glutamate required for synthesis of proteins and collagen (**Rath et al., 2014**).

Arginase 1 and arginase 2 are homologous enzymes that convert L-Arginine to urea and L-ornithine and compete with

nitric oxide synthases for L-Arginine. Increased arginase 2 activity may reduce nitric oxide production by the endothelium in disease states including erectile dysfunction. Studies on animal models showed that inhibition of arg activity improve erectile function (**Pernow and Jung, 2013**).

The aim of this work was to assess serum arginase 2 level in patients with vasculogenic erectile dysfunction.

## PATIENTS AND METHODS

### This study included two groups:

- Group I: Forty individuals with vasculogenic erectile dysfunction.
- Group II: Forty ages matched healthy individuals as controls.
- The patients were from Andrology outpatient clinic of Al-Azhar University Hospitals.

### Inclusion criteria:

- Age between 30 and 60years.
- Medical diagnosis of erectile dysfunction.

### Exclusion criteria:

- Hormonal disorder (testosterone, pituitary, thyroid hormones) excluded clinically.
- Psychological disorders.
- Neurogenic disorder.
- Hypogonadism.
- Renal failure.
- Liver cell failure.
- Cerebro-vascular accidents.
- Central nervous system trauma.
- Drugs affecting erection.
- Addiction as hashish and bango.
- Penile implant.

- Anatomical abnormality.

Each subject was submitted to personal history, sexual history, past history and international index of erectile function (IIEF-5) questionnaire. Classification of ED was classified into five severity grades, i.e. no ED total score (22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), and severe ED (1-7). Patients with a score of 21 or less may have evidences of ED (*Cappelleri and Rosen, 2005*).

All subjects were submitted to physical examination, penile duplex and serum arginase-2 estimated by ELIZA.

Written informed consents were obtained from all studied subjects after complete description of the study to them.

Results have been summarized using descriptive statistics. These were expressed as mean ± standard deviation (SD). Data were compared by using the

one-way analysis of variance test (ANOVA) followed by post-hoc test. The probability values (P) less than 0.05 was considered significant. All statistical analyses were performed with the aid of Statistical Program for Social Science (SPSS) software version 18.0 (Chicago, Illinois, USA).

### RESULTS

- There was a statistically highly significant (p <0.001) difference between patient group and control group and between different age groups in patient group regarding serum arginase 2 level (Table 1).

**Table (1):** Comparison between serum arginase 2 level in the in the different studied groups.

Parameters	Groups	Patients			P value
		Control	<i>118.08 ± 62.45</i>		
Serum arginase 2	<i>46.23±23.34</i>	Group I (30 to 40)	Group II (40 to 50)	Group III (50 to 60)	<i>&lt; 0.001</i>
		<i>56.00±13.08</i>	<i>92.31±39.72 *#</i>	<i>174.29±43.81 *#</i>	

Values are presented as mean ±SD

\*: Statistically significant compared to corresponding value in control group (P<0.05).

#: Statistically significant compared to corresponding value in group I (P<0.05).

\$: Statistically significant compared to corresponding value in group II (P<0.05).

- There was a statistically highly significant difference ( $P < 0.001$ ) between diabetic and non-diabetic groups in patient group regarding serum arginase 2 level (Table 2).

**Table (2):** Comparison between serum arginase 2 level in the non-diabetic and diabetic groups and between arteriogenic, venogenic and mixed types of vasculogenic ED.

Parameters	Groups		Arteriogenic	Venogenic	Mixed	P value
	Non diabetic	Diabetic				
Serum arginase	64.72±	161.73±	67.31±	112.78±	202.00±	< 0.001
II	26.32	47.38 *	23.15 *#	46.53 *#\\$	37.81 #\\$@	

Values are presented as mean ±SD

\*: Statistically significant compared to corresponding value in non diabetic group ( $P < 0.05$ ).

#: Statistically significant compared to corresponding value in diabetic group ( $P < 0.05$ ).

§: Statistically significant compared to corresponding value in arteriogenic group ( $P < 0.05$ ).

@: Statistically significant compared to corresponding value in venogenic group ( $P < 0.05$ ).

- There was a statistically highly significant difference ( $P < 0.001$ ) in serum arginase 2 level regarding severity of erectile dysfunction according to IIEF-5 questionnaire (Table 3).

**Table (3):** Comparison between serum arginase 2 level regarding severity of erectile dysfunction according to IIEF-5 questionnaire and the percentage of each severity to the total number of patients.

Parameters	IIEF-5 QUESTIONNAIRE				P value
	Mild	Mild to moderate	Moderate	Severe	
Serum arginase II	59.17±	101.67±	102.14±	179.20±	<0.001
	23.82	38.30	43.77	43.04 *#\\$	
Percentage %	30%	15%	17.5%	37.5%	

Values are presented as mean ±SD

\*: Statistically significant compared to corresponding value in mild group ( $P < 0.05$ ).

#: Statistically significant compared to corresponding value in mild to moderate group ( $P < 0.05$ ).

§: Statistically significant compared to corresponding value in moderate group ( $P < 0.05$ ).

## DISCUSSION

The current study showed that patients with ED have significant higher concentrations of serum arginase 2. This

result agreed with Na et al. (2014) who found that arginase 2 is constitutively expressed in cells and tissues, and indirectly regulates nitric oxide (NO) generation from nitric oxide synthase

(NOS) by competition for a common enzyme substrate L arginine.

The present study showed marked increase in serum arginase 2 levels with increased age. This result was in agreement with **Mirea et al. (2012)** who stated that aging is associated with changes in arterial wall structure and function. The most frequent modifications are luminal enlargement, vessel wall thickening due to intimal and medial expansion, elastin depletion and fragmentation, collagen and calcium deposition, glycation of proteins, and impaired vasomotor function associated with endothelial dysfunction.

The current study showed that prevalence of ED was more common in diabetic than non-diabetic patients with a percentage of 55% diabetic and 45% non-diabetic. There was a significant correlation between serum arginase 2 level and the disease diabetes mellitus which affected greatly many organs in human body. These results were in agreement with results of study done by **Fiorentino et al. (2013)** who proved that diabetes mellitus (DM) is a worldwide disease that is frequently associated with a high risk of atherosclerosis and renal, nervous system and ocular damage. Oxidative damage is involved in DM and the associated complications, with reactive oxygen species (ROS) being implicated in the pathogenesis of DM. Patients with type 2 DM frequently exhibit vascular endothelium dysfunction associated with hypercholesterolemia, and NO deficiency is a major factor contributing to endothelial dysfunction.

There was also significant difference in serum arginase 2 level between different

types of vasculogenic erectile dysfunction. As regard the prevalence of different vasculogenic types of ED, the highest percentage was to corporovenogenic erectile dysfunction (45%) followed by arteriogenic erectile dysfunction and finally mixed type with the least percentage. Those findings were in agreement with **Forstermann and Sessa (2012)** who explained that the endothelium regulates vascular functions by multiple mechanisms. The decreased bioavailability of the vasoprotective endothelial NO molecule best reflects dysfunctional endothelium or endothelial dysfunction under pathological conditions and in the presence of risk factors. It represents one of the most important early markers and mechanisms of cardiovascular disease and also predicts the future atherosclerotic disease progression.

As regard the International Index of Erectile Function (IIEF-5) Questionnaire, this study showed that an increase in serum Arginase 2 was associated with decrease in IIEF-5 score that reflect an increase in erectile dysfunction and that higher levels of serum Arginase 2 level was in patients with severe ED with IIEF-5 score (5-7) as there was a statistically negative correlation and significant between serum arginase II level and IIEF-5 score with  $p$  value  $< 0.001$ .

Those findings were in agreement with **Rosen et al. (2002)** who stated that the International Index of Erectile Function (IIEF), which consists of 15 items and 5 domains, is a psychometrically valid and reliable instrument that was developed through consultations with an international panel of experts for use in determining efficacy of treatment in

controlled clinical trials. The International Index of Erectile Function (IIEF) is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function. It has been recommended as a primary endpoint for clinical trials of erectile dysfunction (ED) and for diagnostic evaluation of ED severity.

## CONCLUSION

Arginase 2 plays an important role of male sexual health as with increase age more endothelial dysfunction and more erectile dysfunction and arginase 2 being one of the strong contributors for this endothelial dysfunction.

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## مستوي الأرجيناز-2 في مصل الدم في المرضى الذين يعانون من ضعف الانتصاب الناتج عن مشكلة في أوعية القضيب الدموية

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**خلفية البحث:** ضعف الانتصاب له تأثير كبير على نوعية حياة الرجال، وهو مشكلة صحية عالمية كبيرة مع تقديرات انتشارها 33-52%. وعلى الرغم من أن الاعتقاد بأن له أصول نفسية أو عصبية، لكن الأدلة الآن تشير بوضوح إلى أن أكثر الأسباب شيوعاً هو ضعف الانتصاب الناتج عن مشكلة في أوعية القضيب الدموية.

**هدف البحث:** تقييم تأثير مستوى إنزيم أرجيناز-2 في مصل الدم على وظيفة الانتصاب.

**المرضى وطرق البحث:** أجريت الدراسة على 80 فرداً من الحاضرين للعيادة الخارجية للذكورة بمستشفيات جامعة الأزهر تم تقسيمهم إلى مجموعتين متساويتين:

- **المجموعة الأولى:** يعانون من ضعف جنسي ناتج عن مشكلة في أوعية القضيب الدموية.
- **المجموعة الثانية:** من الأصحاء المتناسقين في السن مع المجموعة الأولى كضوابط.

وقد تم إخضاع جميع المرضى لأخذ التاريخ الكامل بما في ذلك التاريخ الشخصي والتاريخ الجنسي، والتاريخ الماضي من اضطرابات طبية أو عمليات. وقد تم تقييم وظيفة الانتصاب معتمداً على المؤشر الدولي للانتصاب وأشعة تليفزيونية علي القضيب، كما تم عمل فحص شامل وفحص للأعضاء التناسلية، وقياس نسبة إنزيم الأرجيناز-2 في مصل الدم.

**النتائج:** هناك فرق ذو دلالة إحصائية عالية بين المرضى والضوابط بخصوص إنزيم الأرجيناز-2 (نانو غرام / مل). وهناك زيادة ملحوظة في مستوى الأرجيناز-2 ومعدل إنتشار الضعف الجنسي مع زيادة العمر. وهناك ارتباط كبير بين مستوى إنزيم الأرجيناز-2 وداء السكري وهناك إختلافات واضحة في مستوى إنزيم الأرجيناز-2 بين الأنواع المختلفة من ضعف الانتصاب الناتج عن مشكلة في أوعية القضيب الدموية. وأعلى نسبة نسبة لعدم القدرة على الانتصاب ناتجة عن التسرب الوريدي (45%)، يليه ضعف الانتصاب الناتج عن مشكلة شريانية في القضيب (32,5%)، وأخيراً النوع المختلط (22,5%). وهناك إنخفاض في درجة الانتصاب حسب المؤشر الدولي للانتصاب وزيادة في ضعف الانتصاب مع الزيادة في إنزيم الأرجيناز-2، وكانت أعلى مستويات إنزيم الأرجيناز-2 في المرضى الذين يعانون من الضعف الجنسي الحاد مع تقييم نقاط (5-7)، كما كان هناك وجود علاقة سلبية ذات دلالة إحصائية بين مستوى أرجيناز-2 والمؤشر الدولي للانتصاب.

**الاستنتاج:** يلعب إنزيم الأرجيناز-2 دوراً هاماً في الصحة الجنسية الذكرية كما هو الحال مع زيادة العمر التي تؤدي إلي تلف في الخلايا البطانية .