# Alterations In Vascular Functions In Experimental Androgen Deprivation

#### Thesis Submitted for Partial Fulfillment of M.D. Degree In Basic Medical Science (Physiology)

*By*:

#### **Ghida Mohamed Hassan**

M.B., B.Ch., MSc Assistant Lecturer, Physiology department Faculty of Medicine, Ain Shams University

#### Under supervision of

#### **Professor Faten Mahmoud Diab**

Professor of Physiology, head of Physiology Department Faculty of Medicine, Ain Shams University.

#### **Professor Mahmoud Hani Ayobe**

Professor of Physiology Faculty of Medicine, Ain Shams University.

#### Professor Amira Metwalli Abdel Rahman

Professor of Physiology Faculty of Medicine, Ain Shams University.

#### **Professor Mona Ahmed Ahmed**

Professor of Physiology Faculty of Medicine, Ain Shams University.

#### Dr. Mohamed Hassan El-Sayed

Lecturer of Physiology Faculty of Medicine, Ain Shams University.

Physiology Department
Faculty of Medicine, Ain Shams University
(2015)

# Acknowledgment

It seems very difficult to select the suitable words to express my deep thanks and gratitude to *ALLAH*.

- **Prof. Faten Díab,** professor of physiology, Ain Shams University: Your brilliant, innovative, and ambitious thinking were the reasons for enriching this work. Your deep sincere guidance supported the whole study.
- *Prof. Mahmoud Haní Ayobe,* professor of physiology, Ain Shams University: No words can express my profound gratitude and ultimate thanks for his endless efforts, care, help in overcoming obstacles and meticulous supervision throughout this study.
- **Prof.** Amira Metwally, professor of physiology, Ain Shams University: Your generous cooperation, kind support and beautiful spirit softened a lot of the work hardness.
- **Prof. Mona A. Ahmed,** professor of physiology, Ain Shams University: Your constructive systematic ideas beside your fruitful advice greatly formulated this work.
- *Dr. Mohamed Hassan,* lecturer of physiology, Ain Shams University: Your effort and help was evident in execution of the practical section of the study.

My deepest gratitude to my colleagues and all members of physiology department. Special thanks for *Prof. Ali Khalifa research unit*, *Biochemistry department*, Ain Shams University for their cooperation.

# التغيرات الوظيفية للأوعية الدموية في حالة النقص التجريبي لهرمون التغيرات الوظيفية للأوعية الذموية

رسالة توطئة للحصول على درجة الدكتوراة في العلوم الطبية الأساسي (الفسيولوجيا)

## مقدمة من الطبيبة ، غيدة محمد حسن

مدرس مساعد بقسم الفسيولوجي كلية الطب\_جامعة عين شمس

## تحت إشراف أ • د • رفاتن محمود دياب

الأستاذ بقسم الفسيولوجي- رئيس قسم الفسيولوجي كلية الطب \_جامعة عين شمس

## أ ٠ د ٠ / محمود هاني أيوب

الأستاذ بقسم الفسيولوجي كلية الطب \_ جامعة عين شمس

### أ ٠ د ٠ / أميرة متولى عبد الرحمن

الأستاذ بقسم الفسيو لوجي كلية الطب \_ جامعة عين شمس

## أ • د • رمني أحمد أحمد

الأستاذ بقسم الفسيولوجي كلية الطب \_ جامعة عين شمس

## د ٠ /محمد حسن السيد حسن

المدرس بقسم الفسيولوجي كلية الطب \_ جامعة عين شمس قسم الفسيولوجي كلية الطب \_ جامعة عين شمس (٢٠١٥)



## **Contents**

	Page
Introduction	1
Aims of the work	4
Review of literature	5
• Androgens	5
Androgen deprived state	8
Androgens and hypertension	12
Androgens and baroreceptor reflex	22
Androgens and the antioxidant activity	25
Androgens and lipids	29
Materials and Methods	32
Results	73
Discussion	165
Summary and Conclusion	193
References	200
Arabic Summary	

# **List of Tables**

## • Responses in the 4-weeks orchidectomized rats

Tables	No.	Page
Changes in body weight	1-3	74-77
Changes in plasma androgens	4-6	79-82
Changes in ECG parameters	7-9	83-86
Basal blood pressure and heart rate	10-12	87-90
Responses to Phenylephrine	13-19	92-99
Responses to sodium nitruprusside	20-26	101-108
Maximal responses of systolic blood pressure,	27-29	109-112
heart rate and baroreflex calculated gain		
Vascular reactivity of aortic rings	30-32	116-119
Changes in plasma catalase activity,	33-35	123-126
malondialdhyde levels and aortic tissue nitrate.		

# • Responses in the Finasteride-treated rats

Tables	No.	Page
Changes in body weight	36-38	130-133
Changes in plasma androgens	39-41	135-138
Changes in ECG parameters	42-44	139-142
Basal blood pressure	45-47	143-146
Changes in cardiac weights and their cardiac indices	48-50	147-150
Changes in plasma catalase activity and	51-53	151-154
malondialdhyde levels		
Plasma lipid profile	54-56	158-161

# **List of Figures**

# • Responses in the 4-weeks orchidectomized rats

Figures	No.	Page
Changes in body weight		75
Changes in plasma androgens		80
Changes in ECG parameters	3a,3b	84
Basal blood pressure and heart rate	4	88
Responses to Phenylephrine		93
Responses to sodium nitruprusside		102
Maximal responses of systolic blood pressure, heart rate and baroreflex calculated gain		110
Baroreceptor sensitivity	8	114
Vascular reactivity of aortic rings		116&117
Correlations between plasma total testosterone levels and the aortic ring responses to PE, Ach, ACh/ PE.		121 &122
Changes in plasma catalase activity, malondialdhyde levels and aortic tissue nitrate.	13	124
Correlations between plasma total testosterone levels and plasma catalase activity, malondialdhyde levels and aortic tissue nitrate.	14	128

# • Responses in the Finasteride-treated rats

Figures	No.	Page
Changes in body weight		131
Changes in plasma androgens		136
Changes in ECG parameters		140
Basal blood pressure		144
Changes in cardiac weights and their cardiac		148
indices		
Changes in plasma catalase activity and		152
malondialdhyde levels		
Correlations between plasma total testosterone		156&157
levels, plasma dihydrotestosterone levels and		
plasma catalase activity, malondialdhyde levels		
Plasma lipid profile	23	159
Correlations between plasma total testosterone	24-25	163&164
levels, plasma dihydrotestosterone levels and		
plasma triglycerides, plasma total cholesterol, low		
density lipoprotein-cholesterol, plasma high density		
lipoprotein-cholesterol, and atherogenic index (AI).		

## **List of Abbreviations**

5 α- R	5-alpha-reductase
ACh	Acetylcholine
AI	Atherogenic index
ALT	Alanine amino transferasre
Ang II	Angiotensin II
APD	Action potential duration
APD <sub>20</sub>	20% action potential duration
APD <sub>90</sub>	90% action potential duration
At	Atria
ATP	Adenosine triphosphate
BCG	Baroreflex calculated gain
bpm	Beat per minute
BW	Body weight
CAT	Catalase
COX-2	Cyclooxygenase enzyme-2
CRP	C-reactive protein
DBP	Diastolic blood pressure
DHT	Dihydrotestosterone
DHT/ Total T	Dihydrotestosterone: total testosterone
DNA	Deoxyribonucleic acid

eNOS	Endothelial nitric oxide synthase
FAD	Flavin adenine dinucleotide
FBW	Final bodyweight
FBMI	Final body mass index
Free T	Free Testosterone
Free T/ Total T	Free testosterone: total testosterone
GPX	Glutathione peroxidase
$H_2O_2$	Hydrogen peroxide
HALO	Hours after light on
HDL	High density lipoproteins
HL	Hepatic lipase
HR	Heart rate
IBMI	Initial body mass index
IBW	Initial body weight
I <sub>KUR</sub>	Ultra-rapid delayed K <sup>+</sup> rectifier current
Kv	Voltage gated K channels
LDL	Low density lipoproteins
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
LV	Left ventricle
MABP	Mean blood pressure

MDA	Malondialdhyde
Mx	Maximum
Na <sub>2</sub> EDTA	Disoduim ethenyl diamine tetra acetate
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
ORX	Orchidectomized
PE	Phenylephrine
PGE <sub>2</sub>	Prostanglandin E <sub>2</sub>
PGF <sub>2</sub> α	Prostanglandin $F_2 \alpha$
$\mathbf{PGI}_2$	Prostanglandin I <sub>2</sub> (prostacyclin)
r	Correlation coefficients
ROS	Reactive oxygen species
RV	Right ventricle
SBP	Systolic blood pressure
SNP	Sodium nitruprusside
SOD	Superoxide dismutase
TC	Total cholesterol
TG	Triglycerides
Total T	Total testosterone
$TXA_2$	Thromboxane A <sub>2</sub>
U/L	Unit/ Liter
WH	Whole heart

Δ Deita change	Δ	Delta change
----------------	---	--------------

### Aims of the work

#### The present study was designed:

I- To investigate the mechanisms underlying vascular dysfunction in androgen-deprived state induced by orchidectomy. Vascular functions were studied <u>invivo</u> by assessment of the baroreceptor sensitivity and their responses to pressor and depressor agents. The vascular reactivity of isolated aortic rings in the orchidectomized rats were examined <u>in vitro</u> in order to determine their contractile and relaxant responses to vasoactive agents. Also, the aortic tissue nitrate, the metabolic end product of nitric oxide, as well as oxidant/ antioxidant status were assessed in the orchidectomized rats.

II- To shed light on the cardiovascular risk factors associated with androgen-deprived state induced by finasteride treatment, including determination of oxidant/antioxidant status and plasma lipid profile.