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Hematological and Biochemical Studies on the Effect of Statins (Lipitor) on Male Albino Rats

A Thesis

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Dedication

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List of Abbreviations

Abbr.	Full-term
ADP	Adenosine diphosphate
AI	Atherogenic index
APC	Activated protein C
Apo A-I	Apolipoprotein A-I
Apo A-II	Apolipoprotein A-II
APTT	Activated partial thromboplastin time
AT III	Antithrombin activity
AT1	Angiotensin type1 receptor
ATP ase	Adenosine triphosphatase
CBC	Complete blood picture
CE	Cholesterol esterase
CHD	Coronary heart disease
CO	Cholesterol oxidase
CRI	Coronary artery index
CYP2C9	Cytochrome P2C9
CYP3A	Cytochrome P3A
CYP3A4	Cytochrome P3A4
CYP450	Cytochrome P450
DHBS	3,5-dichloro-2-hydroxybenzenesulfonic acid
DSBmT	N,N-bis (4-sulpho butyl)-m-Toluidine-disodium
EDTA	Ethylenediaminetetraacetic acid
eNOS	Endothelial nitric oxidase
EPCR	Endothelial cell protein C receptors
ET-1	Endothelin-1
FDP	Fibrin degradation products
FFAs	Free fatty acids
FIB	Fibrinogen
Fig	Figure
FPP	Farnesylpyrophosphate
GG	Geranylgeranyl
GGPP	Geranylgeranylpyrophosphate

GGTI	Geranylgeranyl transferase inhibitor
GK	Glycerol kinase
GPO	Glycerophosphate oxidase
GTP	Guanosine triphosphate
HCD	High cholesterol diet
HDL-C	High Density LipoproteinCholesterol
HDLD	High Density Lipoprotein Cholesterol detergent
HGB	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPO	Horseradish Peroxidase
IL	Interleukin
INR	International normalized range
L0	Liquid ordered
LA	Lupus anticoagulants
Ld	Liquid domains
LDL-C	Low Density Lipoprotein Cholesterol
LDLD	Low Density Lipoprotein Cholesterol detergent
LfA-1	Leukocyte function antigen-1
LPS	Lipopolysaccharide
mg/dl	Milligram/deciliter
mg/kg	Milligram/kilogram
MHC	Major histocompatibility complex
MI	Myocardial infarction
min	Minute
MM	Mill mole
ND	Normal diet
nm	Nanometers
NO	Nitric oxide
PAI-1	Plasminogen activator inhibitor-1
PAR-1	Plasminogen activator receptor-1
PAS	Periodic Acid-Schiff
PBS	Phosphate buffer saline
PL	Phospholipid
PLT	Platelets
PMSF	Phenyl methyl sulfonylflouride
PMV	Platelets mean volume

PP	Pyrophosphate
PT	Prothrombin time
PTT	Partial thromboplastin time
PVD	Peripheral vascular disease
RBCs	Red blood cells
RCT	Reverse cholesterol transport
RDW	Red cell distributionwidth
rpm	Revolutions per minute
RVV	Russell's viper Venom
TAFI	Thrombin2 activatable fibrinolysis inhibitor
TC	Total cholesterol
TF	Tissue factor
TFPI	Tissue factor pathway inhibitors
TG	Triglyceride
TM	Thrombomodulin
TNF	Tumor necrosis factor.
t-PA	Tissuetype plasminogen activator
TXA2	Thromboxane A2
VLDL	Very Low Density Lipoprotein Cholesterol
WBCs	White blood cells
α2AP	Alpha-2 antiplasmin
4-AAP	4-aminoantipyrine.

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Abstract

Atorvastatin (Lipitor) is one of the statins that have been known for their lipid-lowering effects, as well as their pleiotropic functions. The current study aimed to evaluate some pleiotropic effects of 20, 40, and 80 mg/kg b.wt of atorvastatin, orally administered tohypercholesterolemicmale rats, daily for 4 weeks. The changes in body weights were tracked throughout the experiment. The study investigated serum lipid profile, atherogenic and coronary artery indices. Regarding erythrocytes membranes fluidity, erythrocytes membrane lipids and cholesterol were estimated, in addition to complete blood count and coagulation tests including, prothrombin time and partial prothrombintime. The Anticoagulant factors fibrinogen, antithrombin III, protein C, and protein S were also assessed. High-intense doses (40 and 80 mg/kg b.wt) of atorvastatin attenuatedobesity, hypercholesterolemia, hypertriglyceridemia and LDL-C concentrations. Moreover, these doses of atorvastatin reduced erythrocytes membranes lipid and cholesterol levels. Further, both doses attenuated antithrombin III, protein-C and-S, and platelets count in comparison with untreated hypercholesterolemic rats. In conclusion, high-intense doses of atorvastatin exhibited anti-obesity and lipid-lowering effects. Moreover, these doses also showed pleiotropic potentials represented by improvement of fluidity of erythrocytes membranes, reduction of coagulation and thrombosis development, which would prevent future incidence of stroke and other cardiovascular diseases.

Key words: Atorvastatin, Hypercholesterolemia, Erythrocytes membranes, fluidity, antithrombotic effect.

Introduction

Obesity is correlated to increased inflammatory cytokines as well as a hypercoagulability status, which results in impairment in vascular and cardiac functions. Inhibiting those factors through therapeutic implications would attenuate theexpected metabolic derangements **(Dirlewanger*et al.*, 2015),** such as: atherosclerosis, hypertension, and other lipids abnormalities. There are many drugs for treatment of hypercholesterolemia, but statins are the most common drug. Statinsarethe 3-hydroxy-3-methylglutaryl (HMG)-Coenzyme A reductase inhibitor and have been evidenced to be potentagents in the management of hyperlipidemia **(Miyagishima *et al.*, 2007)** and in the prevention of atherosclerotic vascular disease, especially coronary artery disease **(Morrissey, 2009).**

Statins exhibit several vascular effects, including antithrombotic properties that are not related to changes of lipid profile. Abundant experimental and clinical evidence has resulted in the widely accepted concept of cholesterol-independent pleiotropic effects produced by statins that include alteration of endothelial dysfunction, leading to increased nitric oxide (NO) bioavailability **(Undas *et al.*, 2005**), regulation of angiogenesis, and reduction of inflammatory response via binding to novel allosteric site within the leukocyte function antigen-1-(LfA-1)-mediated