

**Comparative Study between the Urodynamic
Effects of Anti-muscarinic Drugs and the
Possible Urodynamic Effects of Nicorandil and
Carbamazepine on Over Active Bladder
Induced By Type-1 Diabetes Mellitus
[Experimental and Clinical Study]**

Thesis

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Abstract

Background: Overactive bladder (OAB) is a common clinical problem.

Materials and methods: **Experimental study:** seventy two adult male albino rats weighing 250-300 g, were classified into six groups. Blood glucose, cystometry, dose concentration response to Ach and histopathological examination were done. **Clinical Study:** The study was conducted on fifty with type-1 diabetes mellitus and over active bladder divided into five groups. Urodynamic studies were done and voiding diary and lower urinary symptom sheet was collected from each patient before and after treatment.

Results: **Experimental findings:** Diabetic rats exhibited a significant increase in the intravesical pressures, in tonic contractions to submaximal dose of ACh. and in bladder weight/body weight ratio and musculosa thickness compared to control group, while a significant reduction in those parameters were found in diabetic treated groups to diabetic group. For bladder volume, Oxybutinin and Tolterodine showed significant decrease while Nicorandil and Carbamazepine groups showed significant increase. **Clinical findings:** in Oxybutinin, Tolterodine groups urodynamic parameters and bladder capacities were significantly changed compared to placebo group while insignificant change were found in Nicorandil and Carbamazepine groups. *Conclusion:* Carbamazepine and Nicorandil potentially suppress the overactive bladder resulted from diabetes as shown in experimental work. On the other hand the clinical study didn't show a significant role for both drugs which needs further clinical trials with a more objective investigation.

Key words: Overactive bladder-Diabetes-Oxybutinin-Tolterodine-Carbamazepine-Nicorandil

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List of Abbreviations

+IWT: positive ice-water test
°C: celsius degree
5-HMT: 5-hydroxymethyl tolterodine
Ach: acetylcholine
AR: adrenergic receptor
ATP: adenosine triphosphate
BP: basal pressure
BPH: benign prostatic hyperplasia
BTX: botulinum toxin
Ca²⁺: calcium
cc: cubic centimeter
cGMP: cyclic guanine monophosphate
Cl: chloride
cmH₂O: centimeter water
CNS: central nervous system
CPGA: 2-cyclohexyl-2-phenylglycolic acid
CYP: cytochrome P
DBD: diabetic bladder dysfunction
DIU: sucrose-induced diuresis group
dl: deciliter
DM: diabetes mellitus
DNA: deoxyribonucleic acid
DRG: dorsal root ganglion
EC₅₀: submaximal concentration

ENaC: epithelial sodium channel
EP1: prostaglandin E receptor
ER: extended release
F: french
FD: first desire
FDA: food and drug administration
g: gram
h: hour
H⁺: hydrogen
ICS: International Continence Society
IDDM: insulin dependent diabetes mellitus
IVP: intravesical pressure
IVPRs: intravesical pressure rises
K⁺: potassium
Kg: kilogram
L: leakage
L: lumber
M: muscarinic
MCC: maximum cystometric capacity
Mg: magnesium
min: minute
ml: milliliter
mM: millimole
mmHg: millimeter mercury
MP: maximum pressure
NA: noradrenaline
Na⁺: sodium

NAD⁺: nicotinamide adenine dinucleotide

NaH₂ PO₄: sodium dihydrogen phosphate

NaHCO₃: sodium bicarbonate

NANC: non-adrenergic non-cholinergic

Na_v : voltage-gated Na⁺ channels

ND: normal desire

NGF: nerve growth factor

NO: nitous oxide

OAB: overactive bladder

OTG: oxybutinin transdermal gel

Oxo: oxotremorine

P2X: ligand gated purine receptor

P2Y: G-protein bound purine receptor

p_{abd}: abdominal pressure

PAG: peri-aqueductal grey nucleus

p_{det}: detrusor pressure

PGs: prostaglandins

PMC: pontine micturition center

PSC: pontine urine storage center

p_{ves}: intravesical pressure

RTX: RTX: resiniferatoxin

s.c: subcutaneous

S: sacral

s: second

SCI: spinal cord injury

SD: standard deviation

SD: strong desire

SHR: spontaneous hypertensive rats

STZ: Streptozotocin

Th: thoracic

TP: threshold pressure

trKA: neurotrophic tyrosine kinase receptor type 1

TRP: transient receptor potential

TRPV1: transient receptor potential channel vanilloid type1

U: urgency

UD: urinary diversion group

ug: microgram

WKY: Wistar Kyoto

α : alpha

β : beta

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Introduction

Urinary bladder plays the major role in urine storage and voiding. Its functioning is regulated by the peripheral and central nervous system. Micturition starts with sensing bladder filling, transferring data to the central nervous system processing center and efferent pathways resulting in the voiding response. Increasing the volume of the urinary bladder provokes afferent signals to the central nervous system. The molecular basis of distention sensing involves the urothelium as a major factor during this process (*Saeid and Ismail, 2010*).

Bladder urothelium is the interface between the lumen of the urinary tract and underlying tissues. It forms an active participant in normal bladder function. It exists as an integral part of a sensory web, in which it communicates the degree of bladder filling to the underlying nervous and muscular tissues, and affects their function. This communication is made possible by the urothelial input and output pathways, which allow it to respond to its chemical and physical environment, and engage in multidirectional communication with neighboring cells in subadjacent tissues (*Daneshgari et al., 2009*). Bladder urothelial abnormalities may impact lower urinary tract function by altering the release of mediators and sensory fiber excitability in the bladder. Also, because many of these urothelial functions may be altered in diabetes cases, defects in urothelial cells may in part underlie changes such as detrusor instability and/or changes in bladder capacity (*Hanna-Mitchell et al., 2013*).