DISSERTATION ON

"A STUDY ON SERUM PROLACTIN LEVELS IN CKD PATIENTS & IT'S CORRELATION WITH CORONARY ARTERY HEART DISEASE"

DISSERTATION SUBMITTED TO

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In Partial Fulfilment Of The Regulations

For The Award Of The Degree Of

M.D. - GENERAL MEDICINE- BRANCH – I

THANJAVUR MEDICAL COLLEGE,

THANJAVUR – 613 004.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032.

APRIL - 2015

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON SERUM PROLACTIN LEVELS IN CKD PATIENTS &IT'S CORRELATION WITH CORONARY ARTERY HEART DISEASE"** is the bonafide original work of **Dr.CHANDRAMOULI.R.K** in partial fulfilment of the requirements for M.D Branch -I (General Medicine) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2015. The period of study was from **2014 JANUARY TO 2014 AUGUST**

Prof. Dr. D.NEHRU, M.D.,D.M.R.D,
Unit Chief M-5,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004

Prof.Dr.P.G.SANKARANARAYANAN,M.D.,
Head of the Department,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

PROF.DR.P.G.SANKARANARAYANAN, M.D.,
DEAN I/C,
THANJAVUR MEDICAL COLLEGE, THANJAVUR – 613 004

DECLARATION

I, **Dr.R.K.CHANDRAMOULI.R.K** , solemnly declare that the dissertation titled dissertation on **"A STUDY ON SERUM PROLACTIN LEVELS IN CKD PATIENTS &IT'S CORRELATION WITH CORONARY ARTERY HEART DISEASE"** is a bonafideworkdone by me at Thanjavur Medical College, Thanjavur during Janauary 2014 – August 2014 under the guidance and supervision of **Prof.Dr.D.NEHRU, M.D.,D.M.R.D,** Unit Chief M-5, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to TamilnaduDr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. degree (Branch -I) in General Medicine**.

Place: THANJAVUR.

Date:

Dr. R.K.CHANDRAMOULI
Postgraduate Student,
M.D. in General Medicine,
Thanjavur Medical College,

ACKNOWLEDGEMENT

I gratefully acknowledge and my sincere thanks to the Dean, **PROF.DR.MAHADEVAN,MS** Thanjavur Medical College, Thanjavur, for allowing me to do this dissertation and utilize the institutional facilities.

I am extremely grateful to **Prof.DR.P.G.SANKARANARAYANAN.M.D,** Head of the Department, Department of Internal Medicine, Thanjavur Medical College, for his full-fledged support throughout my study and valuable suggestions and guidance during my study and my post graduate period.

I am greatly indebted to **PROF.DR.D.NEHRU, M.D.,,D.M.R.D,** my Professor and Unit Chief, who is my guide in this study, for his timely suggestions, constant encouragement and scholarly guidance in my study and post graduate period.

I Profoundly thank my professors **PROF.DR.K.NAGARAJAN,M.D PROF.DR.S.MANOHARAN,M.D;,DR.C.GANESAN,M.D,AND DR.GUNASEKARAN,M.D D.M.,** (Registrar), for their advice, guidance and valuable criticism which enabled me to do this work effectively.

I would like to express my gratitude to **PROF.DR.D.RAJENDRAN, MD DM** Department of Nephrology for his immense help in the study which enabled me to complete this work and also permitting me to utilize the facilities available in the department.

My sincere thanks to assistant professors **DR.D.SEKAR,M.D,D.M Dr.KAVITHA,M.D.,**; **DR.K.MUTHUSELVAN,M.D,** for their motivation, encouragement and support. .

A special mention of thanks to all the patients who participated in this study for their kind cooperation without whom the study would not be possible.

I would like to thank my colleagues and friends who have been a constant source of encouragement..

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA-613 001

(Affiliated to the T.N.Dr.MGR Medical University, Chennai)

INSTITUTIONAL ETHICAL COMMITTEE

CERTIFICATE

Approval No. : 074

This is to certify that The Research Proposal / Project titled

A STUDY ON SERUM PROLACTIN LEVELS IN CKD PATIENTS AND ITS CORRELATION WITH CORONARY ARTERY HEART DISEASES

submitted by Dr. R. K. CHANDRAMOULI **of**

Dept. of GENERAL MEDICINE **Thanjavur Medical College, Thanjavur**

was approved by the Ethical Committee.

Thanjavur

Dated :

THANJAVUR MEDICAL COLLEGE * THANJAVUR-4

Secretary

Ethical Committee

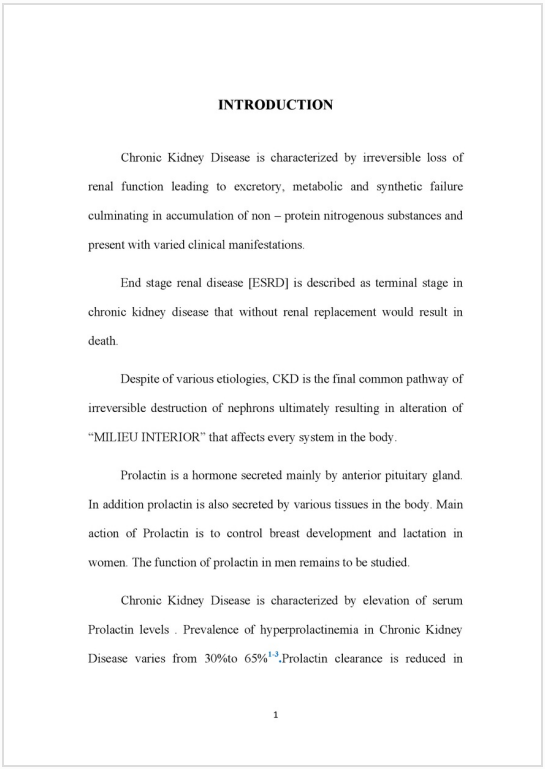
TMC, Thanjavur.

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201211203.md General Medicine CH…
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	“A STUDY ON SERUM PROLACTIN…
File name:	final_chand_1609_-_PRINT.docx
File size:	1.49M
Page count:	107
Word count:	11,084
Character count:	66,880
Submission date:	24-Sep-2014 08:20PM
Submission ID:	450311068



INTRODUCTION

Chronic Kidney Disease is characterized by irreversible loss of renal function leading to excretory, metabolic and synthetic failure culminating in accumulation of non – protein nitrogenous substances and present with varied clinical manifestations.

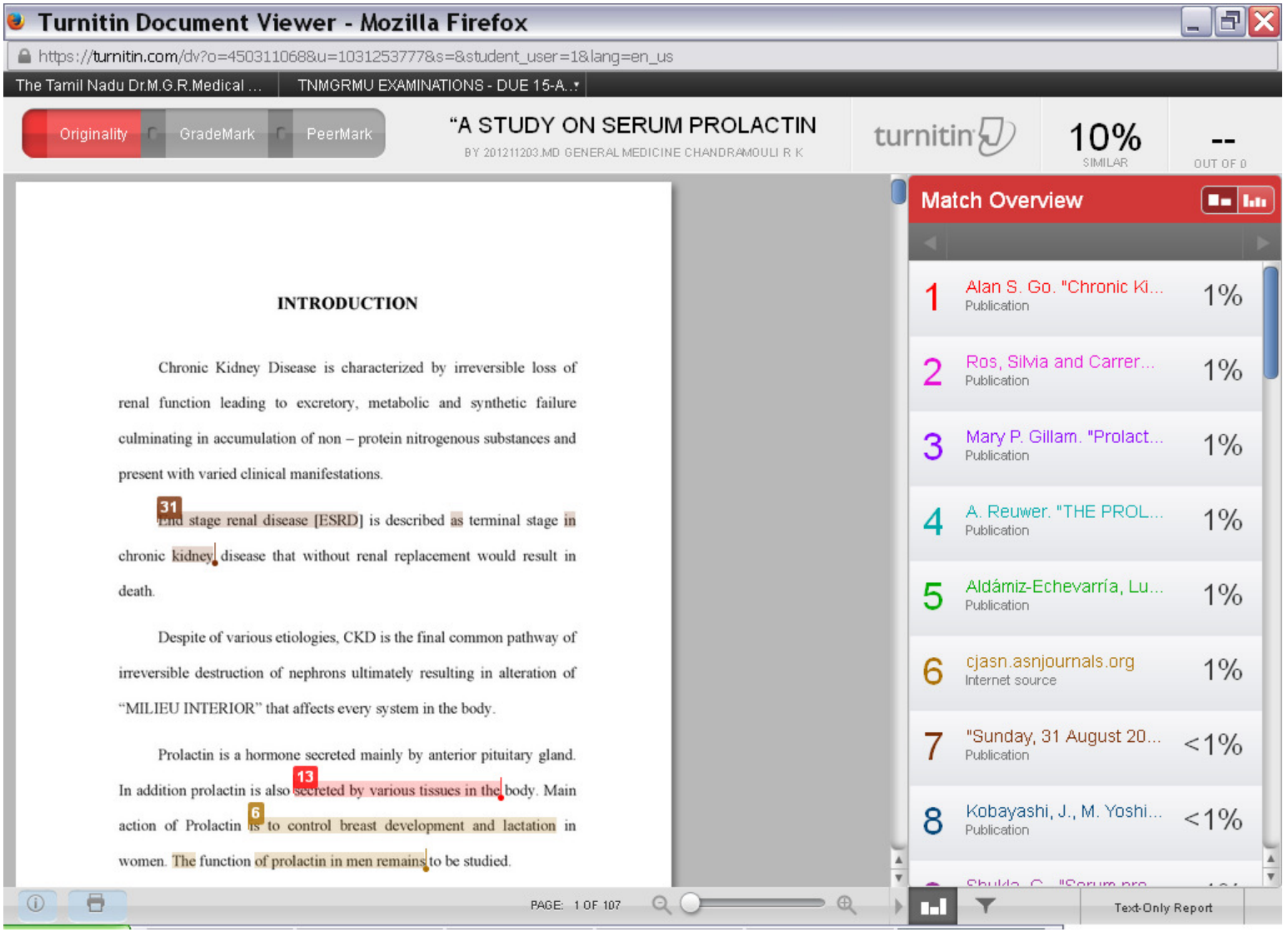
End stage renal disease [ESRD] is described as terminal stage in chronic kidney disease that without renal replacement would result in death.

Despite of various etiologies, CKD is the final common pathway of irreversible destruction of nephrons ultimately resulting in alteration of “MILIEU INTERIOR” that affects every system in the body.

Prolactin is a hormone secreted mainly by anterior pituitary gland. In addition prolactin is also secreted by various tissues in the body. Main action of Prolactin is to control breast development and lactation in women. The function of prolactin in men remains to be studied.

Chronic Kidney Disease is characterized by elevation of serum Prolactin levels . Prevalence of hyperprolactinemia in Chronic Kidney Disease varies from 30%to 65%[1-3].Prolactin clearance is reduced in

1


Turnitin Document Viewer - Mozilla Firefox
https://turnitin.com/dv?o=450311068&u=1031253777&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
TNMGRMU EXAMINATIONS - DUE 15-A..
Originality
GradeMark
PeerMark
"A STUDY ON SERUM PROLACTIN
BY 201211203.MD GENERAL MEDICINE CHANDRAMOULI R K
turnitin
10%
SIMILAR
--
OUT OF 0
INTRODUCTION
Chronic Kidney Disease is characterized by irreversible loss of renal function leading to excretory, metabolic and synthetic failure culminating in accumulation of non – protein nitrogenous substances and present with varied clinical manifestations.
End stage renal disease [ESRD] is described as terminal stage in chronic kidney disease that without renal replacement would result in death.
Despite of various etiologies, CKD is the final common pathway of irreversible destruction of nephrons ultimately resulting in alteration of "MILIEU INTERIOR" that affects every system in the body.
Prolactin is a hormone secreted mainly by anterior pituitary gland. In addition prolactin is also secreted by various tissues in the body. Main action of Prolactin is to control breast development and lactation in women. The function of prolactin in men remains to be studied.
PAGE: 1 OF 107
Match Overview
1 Alan S. Go. "Chronic Ki... Publication 1%
2 Ros, Silvia and Carrer... Publication 1%
3 Mary P. Gillam. "Prolact... Publication 1%
4 A. Reuwer. "THE PROL... Publication 1%
5 Aldámiz-Echevarría, Lu... Publication 1%
6 cjasn.asnjournals.org Internet source 1%
7 "Sunday, 31 August 20... Publication <1%
8 Kobayashi, J., M. Yoshi... Publication <1%
Text-Only Report

CONTENTS

LIST OF TABLES & CHARTS

LIST OF FIGURES

ABBREVIATIONS

PRL	**PROLACTIN**
GH	**GROWTH HORMONE**
HPL	**HUMAN PLACENTAL LACTOGEN**
HCS	**HUMAN CHORIONIC SOMATOMAMMOTROPIN**
cAMP	**CYCLIC ADENOSINE MONO PHOSPHATE**
VIP	**VASO ACTIVE INTESTINAL PEPTIDE**
TRH	**THYROTROPIN RELEASING HORMONE**
kDa	**KILO DALTON**
RIA	**RADIO IMMUNO ASSAY**
IRMA	**IMMUNO RADIO METRIC ASSAY**
ICMA	**CHEMI LUMINO METRIC ASSAY**
NON – REM SLEEP	**NON RAPID EYE MOVEMENT SLEEP**
REM SLEEP	**RAPID EYE MOVEMENT SLEEP**
PIF	**PROLACTIN INHIBITORY FACTORS**
PRF	**PROLACTIN RELEASING FACTORS**
GABA	**GAMMA AMINO BUTYRIC ACID**
DA	**DOPAMINE**
SSRI	**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**
TCAS	**TRICYCLIC ANTI DEPRESSANTS**
TIDA	**TUBERO INFUNDIBULAR DOPAMINERGIC PATHWAY**

GAP	**GONADOTROPIN ASSOCIATED PEPTIDE**
GNRH	**GONADOTROPIN RELEASING HORMONE**
GHRH	**GROWTH HORMONE RELEASING HORMONE**
JAK	**JANUS KINASE**
STAT	**SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION**
CKD	**CHRONIC KIDNEY DISEASE**
GFR	**GLOMERULAR FILTRATION RATE**
VLDL	**VERY LOW DENSITY LIPOPROTEIN**
HDL	**HIGH DENSITY LIPOPROTEIN**
LDL	**LOW DENSITY LIPOPROTEIN**
ESRD	**END STAGE RENAL DISEASE**
RRT	**RENAL REPLACEMENT THERAPY**
PTH	**PARA THYROID HORMONE/PARATHORMONE**
1,25[OH2]D3	**1,25,DIHYDROXY VITAMIN D3**
LH	**LUTEINIZING HORMONE**
IGF	**INSULIN LIKE GROWH FACTOR**
T4	**THYROXINE**
T3	**TRIIODOTHYRONINE**
LHRH	**LUTEINIZING HORMONE RELEASING HORMONE**
CAD	**CORONARY ARTERY HEART DISEASE**
CVD	**CARDIOVASCULAR DISEASE**

ABSTRACT

Background:

In CKD patient's prolactin clearance & production are altered; this causes Hyperprolactinemia in CKD patients.

CKD is associated with increased risk of CAHD.Emerging evidence suggests that prolactin plays a major role in atherosclerotic process.

Objectives:

To study the occurrence of Hyperprolactinemia in CKD patients.

To study the links between hyperprolactinemia in CKD patients & occurrence of CAHD in them.

Methodology:

We conducted an observational study in 50 CKD patients. Fasting serum prolactin levels were measured in them; Incidence of CAHD was evaluated in them using ECG & ECHO.

Results:

In our study among the 50 CKD patients, 28 patients had Hyperprolactinemia which is about 56% of the study population. Statistical analysis using T test showed significant association to exist between Hyperprolactinemia & CKD. In our study among the 28 CKD patients with Hyperprolactinemia 17 patients were diagnosed to have CAHD; this is about 60.7% .Statistical analysis using Chi Square test showed significant association to exist between Hyperprolactinemia in CKD patients & Occurence of CAHD among them.

Conclusion:

Serum prolactin levels are increased in patients with CKD.

This hyperprolactinemia in CKD patients is associated with increased risk of CAHD in them.

Keywords: Prolactin,Hyperprolactinemia,CKD&CAHD.

INTRODUCTION

Chronic Kidney Disease is characterized by irreversible loss of renal function leading to excretory, metabolic and synthetic failure culminating in accumulation of non – protein nitrogenous substances and present with varied clinical manifestations.

End stage renal disease [ESRD] is described as terminal stage in chronic kidney disease that without renal replacement would result in death.

Despite of various etiologies, CKD is the final common pathway of irreversible destruction of nephrons ultimately resulting in alteration of "MILIEU INTERIOR" that affects every system in the body.

Prolactin is a hormone secreted mainly by anterior pituitary gland. In addition prolactin is also secreted by various tissues in the body. Main action of Prolactin is to control breast development and lactation in women. The function of prolactin in men remains to be studied.

Chronic Kidney Disease is characterized by elevation of serum Prolactin levels . Prevalence of hyperprolactinemia in Chronic Kidney Disease varies from 30%to 65%[1-3].Prolactin clearance is reduced in

Chronic Kidney Disease[8]. Prolactin production is altered in Chronic Kidney Disease[9,10].Prolactin's Biological activity is also increased[4].

With progression of Chronic Kidney Disease serum prolactin level also increases. This elevation of serum prolactin level seems to correlate with serum creatinine.

In Male CKD patients Hyperprolactinemia is associated with sexual dysfunction[5]. Hyperprolactinemia is associated with loss of libido .Hyperprolactinemia is associated with impaired erection potency[5]. High prolactin levels may be implicated for this abnormality. This may contribute to gynaecomastia and sexual dysfunction in male CKD patients.

Hyperprolactinemia is also common among female CKD patients. Hyperprolactinemia in female CKD patients is a well – known cause of galactorrhoea and gonadal disturbances with menstrual irregularities, commonly amenorrhoea[5] .Other menstrual irregularities including anovulatory cycles or oligomenorrhoea are more frequent in hyperprolactinemic female CKD patients.

Several studies conducted recently are showing that prolactin may have several biologic actions that participate in the atherosclerotic process. Elevated serum prolactin levels lead to insulin resistance[6].

Hyperprolactinemia is associated with increased inflammatory processes[6]. Elevated serum level of prolactin is associated with endothelial dysfunction[6]. Hyperprolactinemia is found in patients with essential hypertension[7]. Hyperprolactinemia is found during the acute phase of coronary syndromes[11]. Hyperprolactinemia is found during ischemic strokes & transient ischemic attacks[12,13]. Hyperprolactinemia is found in preeclampsia also[14,15]. This hyperprolactinemia is found to play a causative role in the heart failure that accompanies post partum cardiomyopathy[16]. Hyperprolactinemia in men with erectile dysfunction is associated with increased incidence of coronary artery disease[17]. Recent evidences are pointing to the presence of receptors for Prolactin in the atherosclerotic plaques[18,19].

The implications of hyperprolactinaemia in CKD are not well known yet. Chronic Kidney Disease is characterized by accelerated atherosclerotic processes[20,21] .This in long term leads to increased occurrence of coronary artery disease among this population[20,21]. Elevated levels of serum prolactin which occurs in Chronic Kidney Disease may contribute to vascular derangements .This might lead to worse cardiovascular outcomes among CKD patients[4].

This was undertaken as a clinical and biochemical study of serum prolactin levels in CKD patients and the incidence of CAHD among them were assessed in the department of Internal medicine at Thanjavur Medical College Hospital in Thanjavur.

AIMS OF THE STUDY

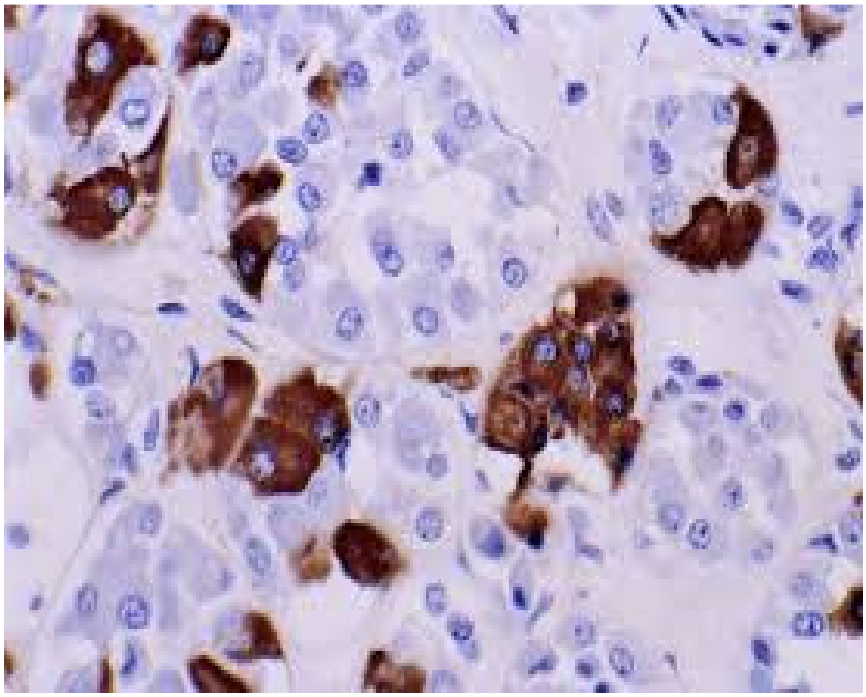
1] To study the association between Chronic Kidney Disease and hyperprolactinemia.

2] To study the incidence of Coronary Artery Heart Disease among the CKD patients with hyperprolactinemia .

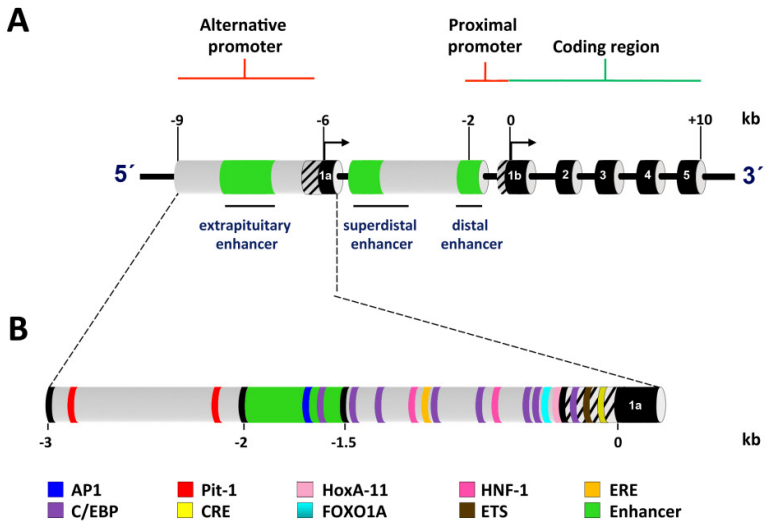
REVIEW OF LITERATURE

CELL OF ORIGIN

Prolactin [PRL] is a 198 – amino acid poly peptide hormone. It's molecular weight is 22000.It is synthesized in the lactotroph cells of pituitary gland .These cells are otherwise called as mammotrophs.In human beings irrespective of sex about 15-25%of pituitary mass is made up of this lactotroph cells[22]. Hyperplasia of these lactotroph cells occur during pregnancy[23,24]. Hyperplasia of lactotroph cells also occur during lactation period[23,24].



PROLACTIN GENE

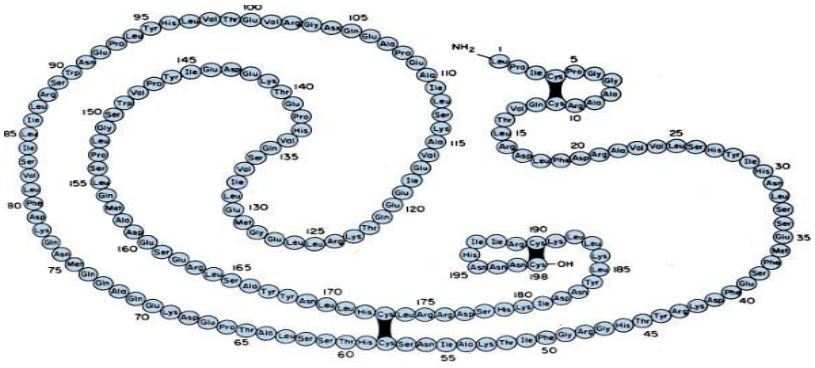


Prolactin gene in the humans is located on chromosome 6[26].Whereas those of related hormones GH and human placental lactogen [HPL, also known as human chorionic somatomammotrophin or HCS] are located on chromosome 17[25].

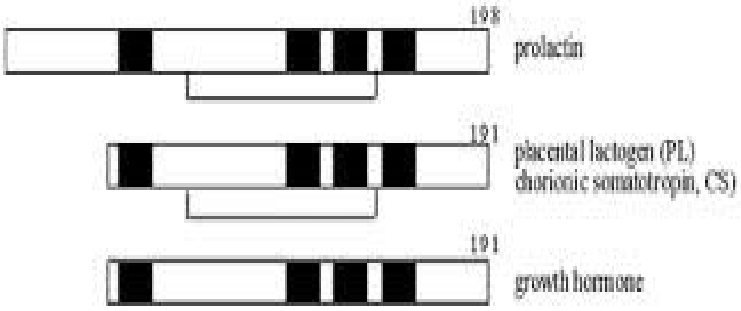
Numbers of factors regulate the transcription of Prolactin gene. Estrogen directly acts on the prolactin gene and facilitates its transcription[27,28].

Thyroid hormone suppresses the prolactin gene transcription both directly and indirectly[29].Glucocorticoids exert an inhibitory action on PRL synthesis and gene transcription[30]. Increase in intracellular cAMP result in an increase in PRL gene transcription[31,32]. Dopamine, acts through the D2 receptor. It leads to inhibition of adenylyl cyclase[33,34].This leads to reduction in the level of intracellular cAMP.VIP stimulates adenylyl cyclase[35].This increases intracellular cAMP level. This leads to Release of prolactin.A number of factors like TRH, Angiotensin II, and Dopamine affect PRL secretion through phosphoinositide / arachidonate pathway[36]. Increase in intracellular calcium level results in PRL gene transcription, PRL synthesis and release.

HORMONE BIOSYNTHESIS



Despite evolution from an ancestral hormone common to GH and human placental lactogen [Hpl], PRL shares only 16% of its residues with former and 13% with hPL.



The primary translation product of the human PRL gene is 227 amino acids in length, consisting of a 28 amino acid signal peptide and a 199 amino acid hormone with a molecular mass of 23 kDa[37].

The Prolactin molecule has three disulfide bonds. This results in folding of the prolactin molecule.The Prolactin molecule undergoes number of post translational modifications. This includes cleavage, polymerization, glycosylation, phosphorylation & degradation. Thus final Prolactin molecule is variable depending on the degree of post translational modifications. Thus different assays for prolactin measurement give various results because of this post translational modification.

GLYCOSYLATED FORMS

Glycosylation of human prolactin occurs[38] .The glycosylated variants account for 13% to 25% of pituitary PRL and 50%to 100% of

circulating PRL[39]. Glycosylated PRLs are less immunoreactive in the routine PRL RIA, bind less well to the PRL receptor and are less bioactive, using a variety of bioassays[40]. Interestingly, during pregnancy, subsequent lactation and pathologic hyperprolactinemic states, when there is a high PRL secretion rate, the relative amount of non glycosylated PRL increases compared to other times.

PHOSPHORYLATED FORMS

Phosphorylated forms of PRL are found in rat and bovine blood. Whether this process occurs in humans is unknown.

Prolactin Synthesis:

Prolactin synthesis occurs in following organs:

Pituitary	Lymphocytes
Deciduas	Leukocytes
Myometrium	Prostate
Breast	

DECIDUAL PROLACTIN

Serum Prolactin levels in mother's blood rise during pregnancy .This Prolactin in mother's blood is secreted by Pituitary gland. High levels of Prolactin concentration are found in amniotic fluid

also[41]. Early biochemical studies found that amniotic fluid PRL was identical to serum PRL biologically, chemically and immunologically[42]. Through several studies it was documented that human deciduas produced PRL and that its bioactivity was equal to pituitary PRL[43].

PROLACIN SECRETION

Following synthesis on rough endoplasmic reticulum, PRL is packaged in to secretory granules in the Golgi apparatus and PRL release occurs via exocytosis.

MEASUREMENT OF PROLACTIN

RADIO IMMUNO ASSAY [RIA][44,45]: These are double antibody assays.
IMMUNO RADIO METRIC ASSAY[IRMA]
CHEMILUMINOMETRIC ASSAY[ICMA]
BIOASSAY: Using Nb2 node rat lymphoma cell assay[46].

PHYSIOLOGY

PATTERN OF PROLACTIN SECRETION:

Pituitary gland secretes Prolactin hormone in a pulsatile manner. The Interval between each pulse of Prolactin hormone secretion is about 8 minutes[47,48].

Prolactin secretion & sleep[49,50]:

Prolactin is secreted in a pulsatile manner 60-90 minutes after the onset of sleep.This increases with non – REM sleep.This fall prior to the next REM sleep.Lowest levels are found during non – REM sleep.The diurnal variation in prolactin secretion is maintained with occurrence of sleep.This is maintained in spite of other physiologic influences like breast feeding.

Prolactin secretion & Food intake[51,52]:

Secretion of hormone Prolactin starts to rise after food intake.Amino acids released from protein digestion cause this increase in secretion.

Prolactin secretion & aging process:

No consistent relationship between prolactin secretion and aging could be established in various studies.

Prolactin secretion & Menstrual cycle[53,54]:

Some studies have shown that higher levels during mid – cycle period. These studies have also shown lower levels during follicular phase compared to luteal phase.

Prolactin secretion & Pregnancy[55,56]:

Prolactin levels progressively increase during pregnancy.This is due to the hormone estrogen.This stimulates the production of prolactin hormone from pituitary.

Prolactin & Lactation[56]:

Suckling from new born baby stimulates release of prolactin hormone from pituitary gland.Prolactin levels gradually return to baseline over few months.

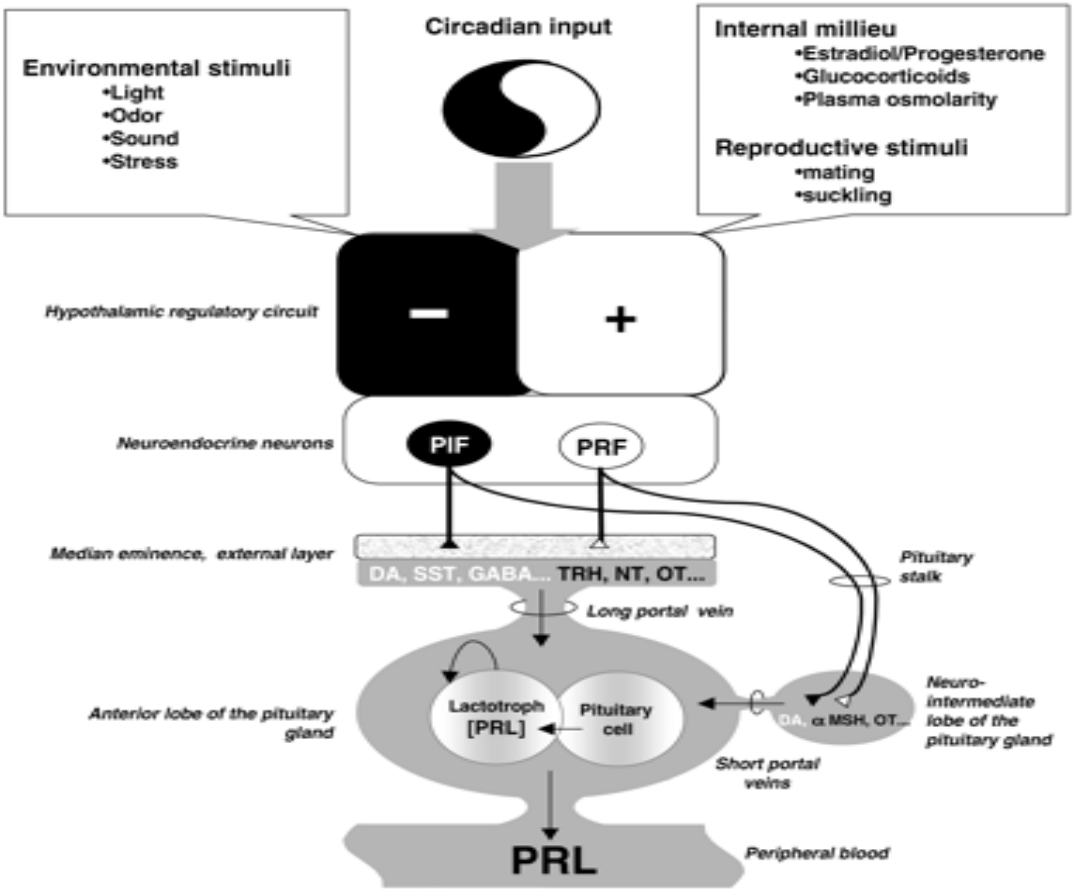
Prolactin & Stress[57]:

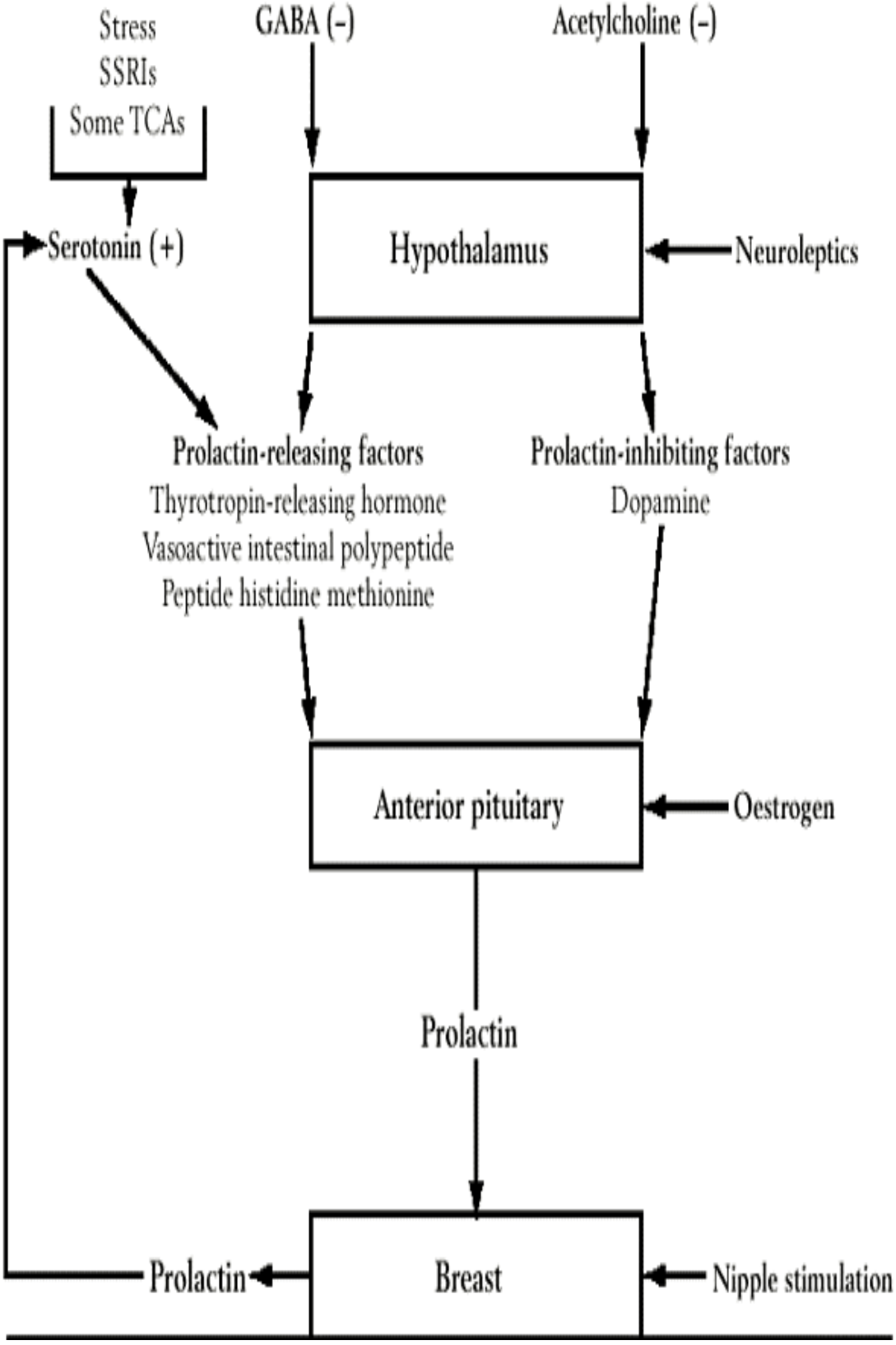
Pituitary releases several hormones in response to varying form of stress.One of the important hormones released by pituitary in response to stress is Prolactin.

Prolactin & Thyroid hormones:

Thyroid hormones act on the lactotroph cells of pituitary and decrease the production and subsequent release of prolactin.Serum levels of prolactin hormone are increased in hypothyroidism.

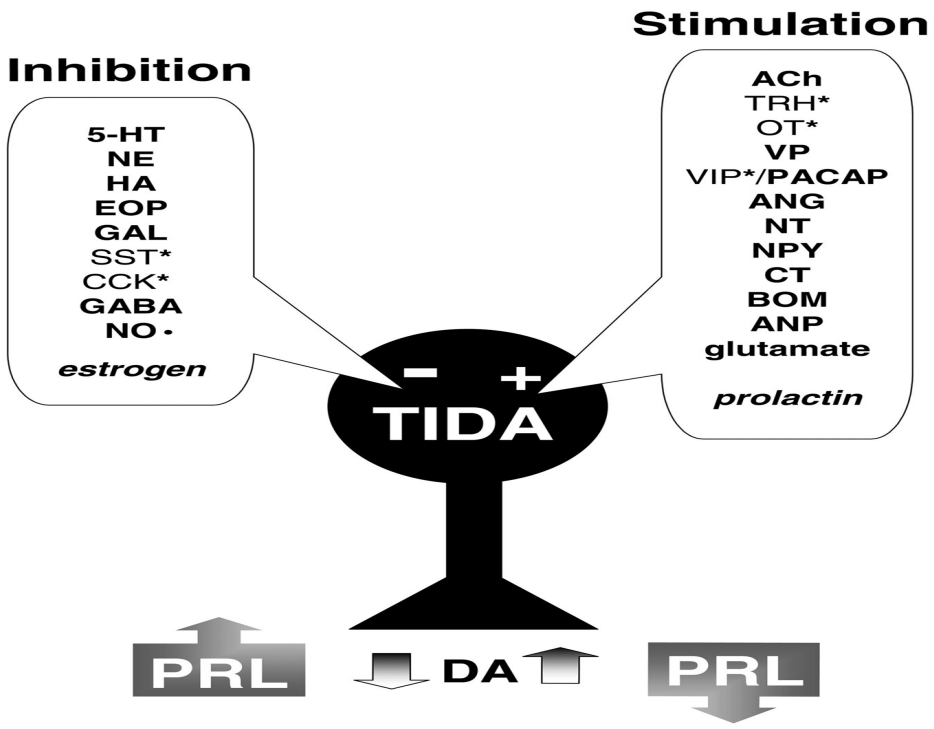
NEUROENDOCRINE REGULATION

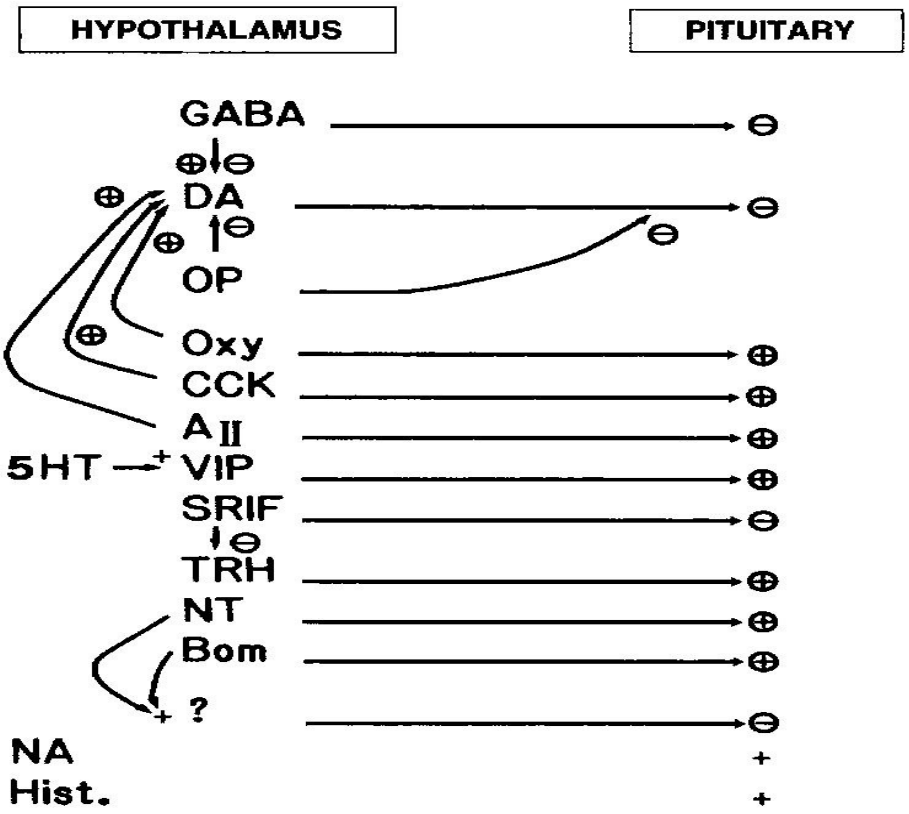



Stress
SSRIs
Some TCAs
GABA (-)
Acetylcholine (-)
Serotonin (+)
Hypothalamus
Neuroleptics
Prolactin-releasing factors
Thyrotropin-releasing hormone
Vasoactive intestinal polypeptide
Peptide histidine methionine
Prolactin-inhibiting factors
Dopamine
Anterior pituitary
Oestrogen
Prolactin
Prolactin
Breast
Nipple stimulation

Disruption of pituitary stalk:

Hypothalamus releases a number of prolactin inhibitory factors.These prolactin inhibitory factors reach Pituitary by Hypothalamo hypophyseal portal vessels.So with disruption of pituitary stalk this negative influence gets released.This leads to increase in the release of Prolactin secretion.





Prolactin Inhibitory Factors [PIFs]

Dopamine[58,59]

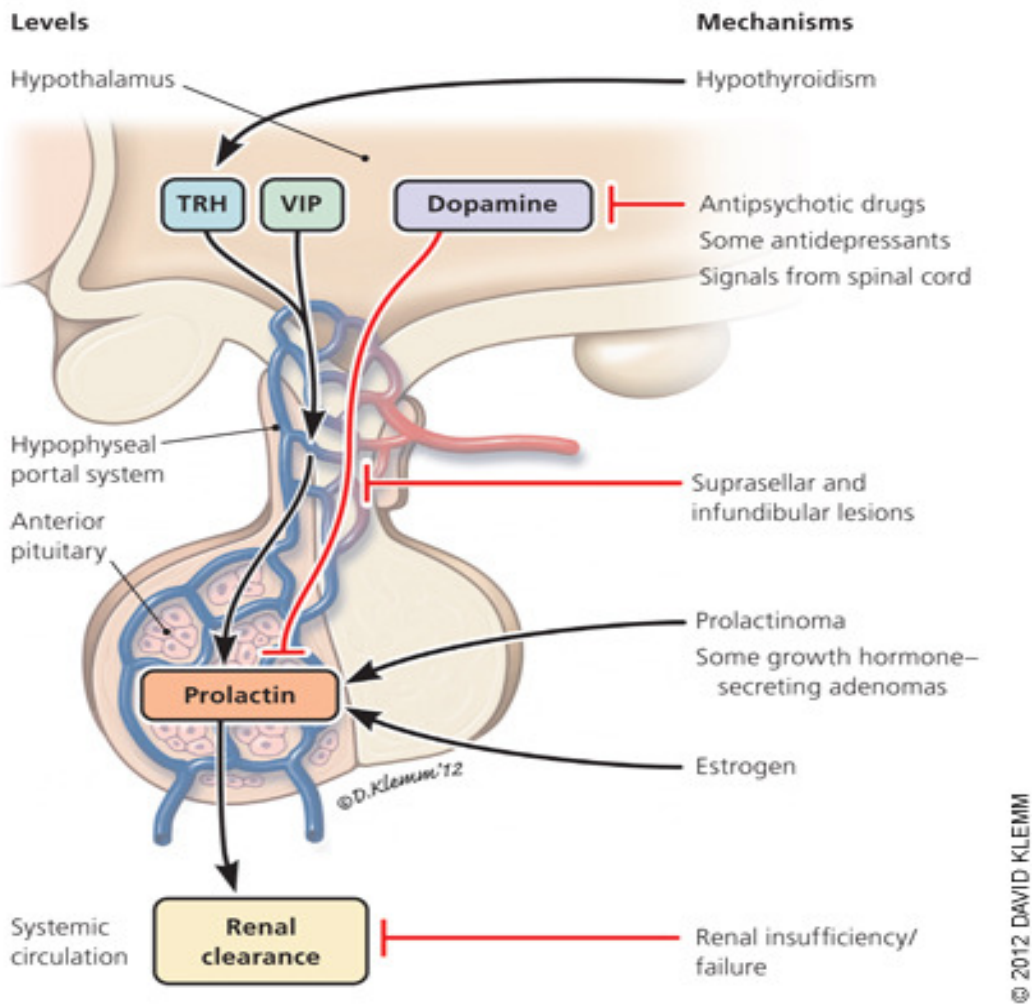
Dopamine is found to have an inhibitory effect on the secretion of hormone prolactin.

Gonadotropin Associated Peptide [GAP]

This is found out to have PRL inhibiting ability in rat experiments.But little is known about its bioactivity in human beings.

Gamma - Amino Butyric Acid[GABA]

Gamma - Amino Butyric Acid causes a reduction in the secretion of Prolactin hormone.



PROLACTIN RELEASING FACTORS

Thyrotropin Releasing Hormone [TRH][60]

Thyrotropin Releasing Hormone plays a facilitatory role in the secretion of hormone prolactin.

Vasoactive Intestinal Peptide [VIP][61]

Vasoactive Intestinal Peptide plays a facilitatory role in the secretion of hormone prolactin.

Peptide Histidyl Methionine

This molecule is a precursor for Vasoactive Intestinal Peptide.This plays a facilitatory role in secretion of prolactin.

Serotonin[62]

Serotonin facilitates release of hormone Prolactin.

Opiod peptides

In humans, Opiod peptides play a minor facilitatory role in secretion of prolactin hormone.

Growth Hormone Releasing Hormone [GHRH]

Under some circumstances Growth Hormone Releasing Hormone facilitates release of prolactin.

Oxytocin and Vasopressin

Oxytocin and Vasopressin may be involved in release of prolactin mediated through VIP.

Gonadotropin Releasing Hormone [63]

In some studies GnRH has been found to facilitate release of prolactin hormone.

PRL – releasing peptide

In some recent studies this peptide has been found to facilitate release of prolactin.

Other neuro active peptides and neurotransmitters

Neurotensin, Substance P, Cholecystokinin, Somatostatin

The above mentioned peptides are found to elevate PRL levels in rats but their relevance to human beings is not known at present.

Histamine[64]

Histamine can cause a rise in PRL secretion in human beings.This is further augmented by H2 blockers and is blocked by H1 blockers.

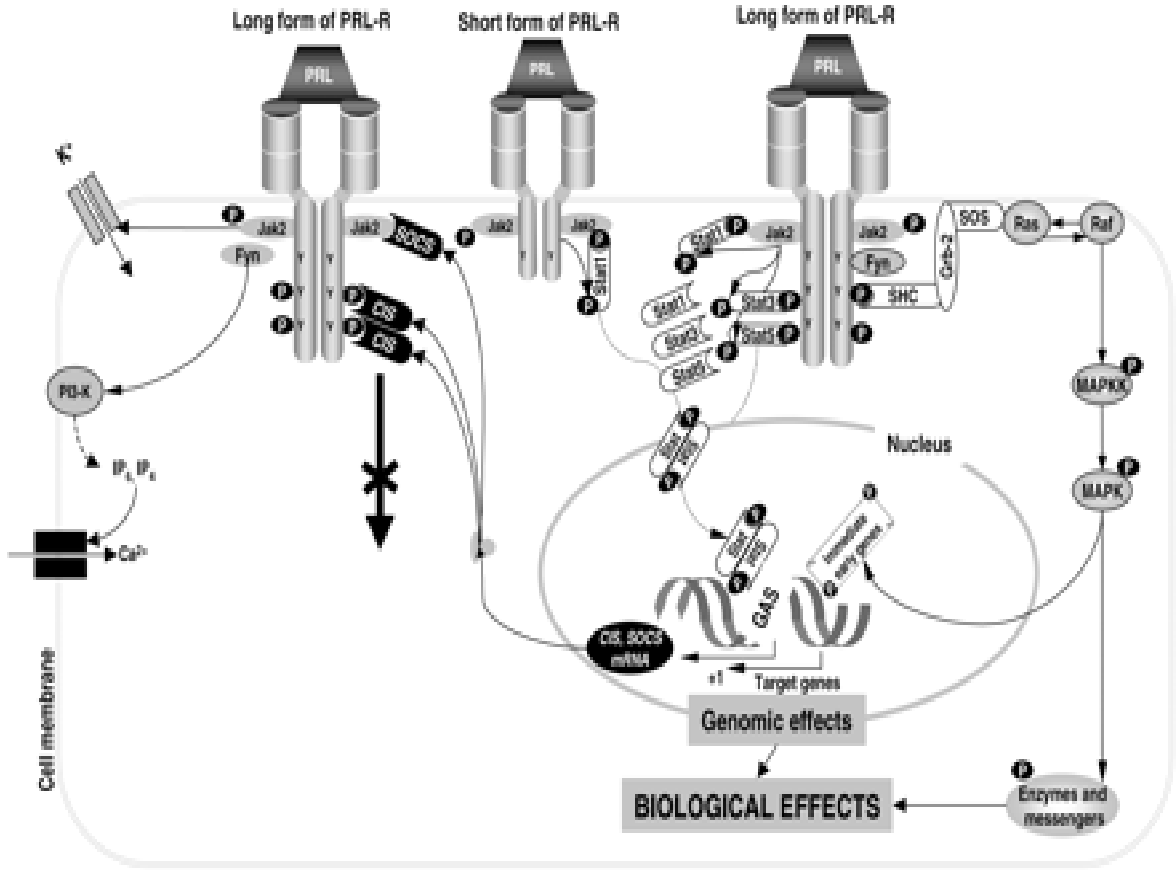
Acetyl choline

From several studies it is learnt that true role of acetyl choline in PRL secretion is unknown.

PROLACTIN ACTION

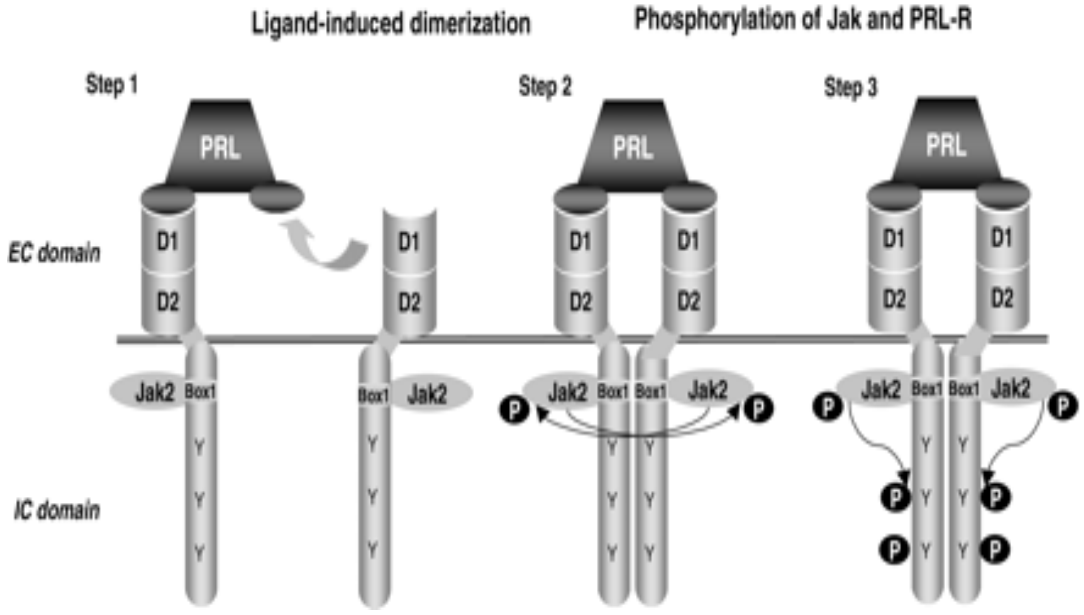
The main function of prolactin in human beings is to facilitate lactation.Prolactin facilitates lactation by aiding in breast development.Various studies are now showing other biological actions for prolactin.But these are yet to be confirmed.

PRL Receptors



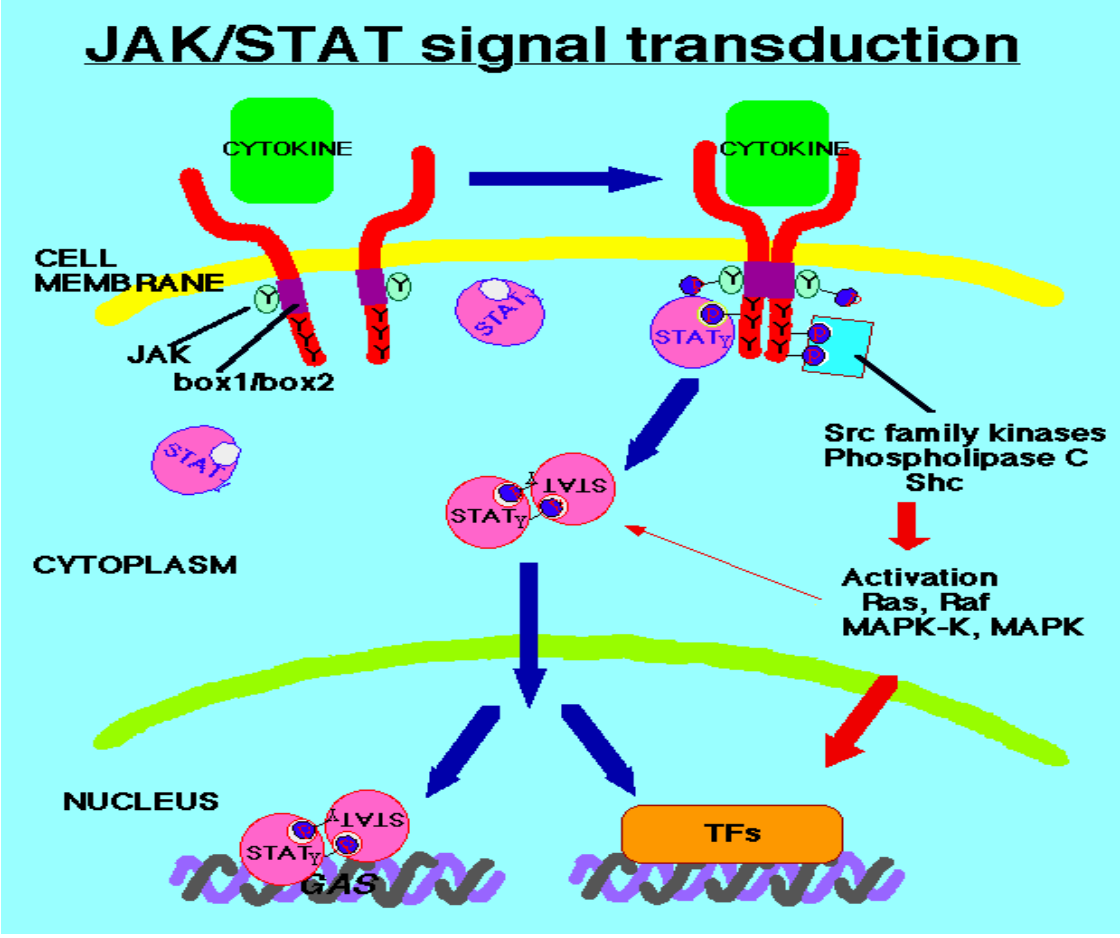
The PRL and GH receptors are members of the class 1 cytokine receptor family.The human genes for the PRL and GH receptors have been localized to the short arm of chromosome 5 , sublocalizing to region 5p13-p14.The human PRL receptor gene has 10 exons ,with exons 3 to 10 encoding the full length of the long arm of the receptor .The human PRL receptor is 598 amino acids long, has a theoretical , non- glycosylated molecular mass of 66.9 kDa and an additional signal peptide of24 amino acids .The extracellular domain contains five cysteine residues and three

potential N- linked glycosylation sites.There is a hydrophobic region corresponding to single transmembrane spanning region of the receptor.The human PRL receptor has a much longer intracytoplasmic region than does the rat PRL receptor but there is high sequence homology between rat ,rabbit and human PRL receptors also between the human PRL and GH receptors. Two isoforms of PRL receptor result from alternative splicing and differ in the length and composition of cytoplasmic tail, being referred to as the long and intermediate forms; the short form found in the mouse is not present in humans.PRL binds to its receptor with high affinity. Once PRL binds to its receptors there is dimerization of the receptor ,a necessary step for activation of receptor.PRL receptors are widely distributed ,being found in the breast , pituitary , liver , kidney tubules , adrenal cortex , prostate , ovary , testes , seminal vesicles , epididymis , intestine , skin , pancreatic islets , lymphocytes , lung , myocardium and brain.PRL release caused by suckling increases PRL receptor levels in the breast and liver , resulting in a much greater PRL binding activity in lactating animals as compared to those not lactating. Hepatic PRL receptor synthesis and numbers increase with estrogen treatment in vivo, mediated by the effect of estrogen on increasing pituitary PRL secretion.



Interaction of PRL binding site 1, encompassing several amino acids belonging to helices one and four, with one PRL receptor causes the formation of a one – hormone – one receptor complex. This is a prerequisite for PRL binding site 2, involving helices 1 and 3, to interact with another receptor, and ultimately causing the formation of the active trimeric complex. Signal transduction of the activated receptor involves the JAK- Stat pathway .JAK 2 is the particular Janus Kinase involved and it is constitutively associated with the PRL receptor.PRL induced dimerization of the two receptor molecules brings the two associated JAK 2molecules close to each other so that they may be activated by

transphosphorylation of tyrosines.The two cytoplasmic domains of the receptor must be strictly identical , and the short receptor functions as a dominant negative isoform which inhibits activation of receptor complex by heterodimerization.The activated JAK 2 phosphorylates tyrosine residues on the receptor itself and on three members of the Stat family of proteins ,Stat 1 , Stat 3 and Stat 5.Subsequently the hormone receptor complex is internalized and localized in the Golgi and vacuoles but the physiologic significance of this beyond degradation and scavenging is not known.



Prolactin effects on Breast[65]

PRL, GH, Cortisol, Insulin, Estrogen, Progesterone and Thyroxine all contribute to breast development.Prolactin facilitates lobular and alveolar tissue development of breast during pregnancy.Once the breast is fully developed and hormonally primed, PRL stimulates the production of milk proteins and other components. Suppression of this physiologic hyperprolactinemia in the puerperium by bromocriptine causes a rapid cessation of milk production.

Prolactin Effects on Gonadotropin Secretion

Increased serum prolactin hormone levels inhibit secretion of gonodotrophic hormones.

Prolactin Effects on the ovary

The roles of hormone prolactin with respect to functions of ovary are less well understood.

Prolactin & Menstrual function[66]

Increased serum levels of hormone prolactin is associated with following abnormalities

- Oligomenorrhoea.
- Amenorrhoea.

- Galactorrhoea.
- Shortened luteal phase.
- Infertility.
- Decreased libido.
- Orgasmic dysfunction.

Prolactin & Function of Testes[67]

Increased serum levels of prolactin are associated with following abnormalities

- Loss of libido.
- Impotence.
- Decreased muscle strength.
- Decreased beard growth.
- Sometimes galactorrhoea occurs.

Prolactin & Cortex of Adrenal gland

The role of prolactin hormone upon the adrenal gland is less well established.

Prolactin & Bones

Prolactin hormone might play a role pertaining to mineral metabolism in bones.Further studies are needed to confirm this

Prolactin & carbohydrate Metabolism

The role of prolactin hormone upon the metabolism of carbohydrates is less well established.Recent studies have found association between increased serum prolactin hormone levels and increased incidence of insulin resistance.The insulin resistance seen in patients with increased serum levels of prolactin tends to normalize with bromocriptine treatment.But further studies are needed to confirm this finding.

Prolactin & Kidney function

A number of studies in humans have failed to document a significant role for PRL in fluid and electrolyte balance of osmotic stimuli for PRL release.

Prolactin & Immune system

The clinical relevance of lymphoblastoid PRL and changes in immune function in normal individuals and those with hyperprolactinemia is still unclear.Nonetheless, the intriguing finding of increased PRL levels in many patients with autoimmune rheumatologic diseases merits continuous study.

PATHOLOGIC STATES OF PROLACTIN SECRETION

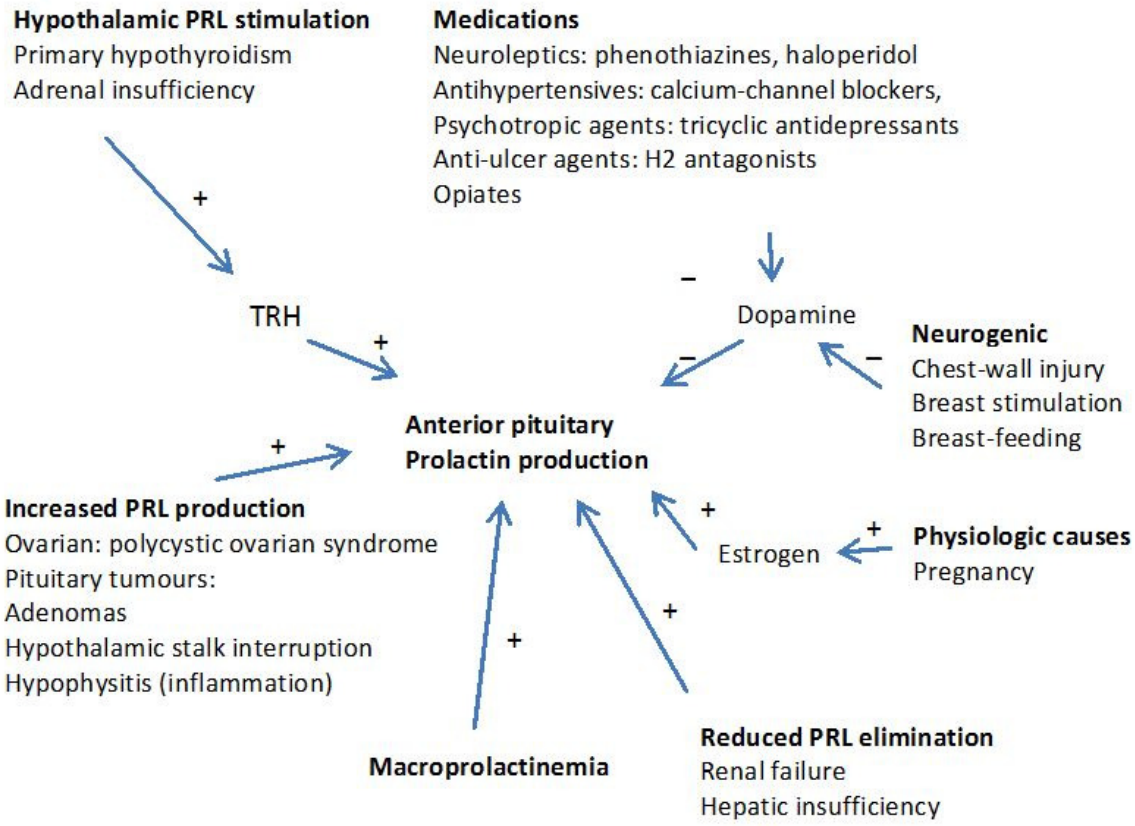
Whenever abnormal serum prolactin levels are detected it should be confirmed by repeating the test two or three times. This is because Prolactin in human beings is secreted in a pulsatile manner.

Hypoprolactinemia

Decreased serum level of hormone prolactin may occur in following situations

- Panhypopituitarism.
- Post partum pituitary necrosis [Sheehan's syndrome].
- Idiopathic [Very rare].

Hyperprolactinemia



Medications

Neuroleptic agents	Phenothiazines. Butyrophenones. Chlorpromazine. Sulpiride. Metoclopramide. Antiemetic agents. Major tranquilizers.
Anti depressants	Tricyclic anti depressants. Mono Amine Oxidase inhibitors. Selective Serotonin reuptake inhibitors.
Opiod drugs	Opiod abuse. Cocaine abuse.
Antihypertensive drugs	Alpha Methyl Dopa. ACE inhibitors: Enlapril. Reserpine.
Calcium Channel Blockers	Verapamil
Anti Retro Viral Therapy	Protease inhibitors.
H2 blockers	Ranitidine, Cimetidine etc.

Stress

The following conditions are reported to be associated with increased serum prolactin levels

- Transient elevations of serum prolactin hormone level occur with physical stress.
- Minimal transient elevations of serum prolactin level are found in association with pschychologic stress.
- Pseudocyesis.

Renal disease[1,2,3&68.]

Elevated serum prolactin levels are found in chronic kidney disease patients.Both male and female patients with chronic kidney disease have elevated serum prolactin levels.The following mechanisms are proposed for the increase in serum prolactin levels seen in patients with chronic kidney disease.There is decreased elimination of Prolactin in patients with chronic kidney disease.The metabolism of hormone prolactin is reduced in patients with chronic kidney disease.Suppression of prolactin hormone in response to dopamine infusion is decreased in patients with chronic kidney disease.Some recent evidences are emerging that production of hormone prolactin is increased in patients with chronic kidney disease.So overall there is disordered regulation of prolactin

hormone synthesis and elimination in patients with chronic kidney disease.But the exact mechanism behind the rise in serum prolactin levels in patients with chronic kidney disease is yet to be identified.Renal transplantation for patients with chronic kidney disease brings the prolactin levels to normal in these patients.The rise in serum prolactin levels seen in patients with chronic kidney disease is a major causative factor for the occurrence of hypogonadism, decreased libido and sexual dysfunction among male CKD patients.Among female CKD patients the rise in serum prolactin levels lead to menstrual irregularities, decreased libido, and orgasmic dysfunction.

Cirrhosis of Liver[69]

Serum levels of hormone prolactin are found to be increased in patients with cirrhosis of liver.Prolactin response to TRH was found to be normal in 75 % of patients with alcoholic cirrhosis .Prolactin response was found to be blunted in the remainder.In one study serum prolactin hormone levels were found to be elevated in patients with hepatic encephalopathy.Defect in the hypothalamic dopamine generation leads to the rise in serum prolactin levels in these patients.

Hypothyroidism[70]

Serum levels of prolactin hormone are increased in patients with hypothyroidism.The following mechanisms are proposed for this.Hypothyroidism leads to rise in the level of TRH.There is increased generation of Vasoactive Intestinal Peptide [VIP] in the pituitary gland.The above mechanisms lead to the rise in the serum levels of hormone prolactin in this group of patients.Treatment with thyroxine brings the serum prolactin hormone levels to normalcy.

Adrenal insufficiency

Very rarely adrenal insufficiency can be associated with increase in the levels of serum prolactin hormone.

Neurogenic[71]

The rise in serum prolactin hormone levels in following situations is because of the stimulation of neuronal pathways that originate in chest wall and course through spinal cord.

- Chest wall lesions.
- Cervical cord lesions.
- Post mastectomy.
- Post thoracotomy.

- Chronic spinal cord injuries.
- Sexual breast stimulation.
- Suckling.

Ectopic Prolactin Secretion

- Ectopic production and secretion of hormone prolactin is very rare.

Diseases of pituitary stalk & Diseases of hypothalamus

In these disorders control of pituitary by hypothalamus is lost.This leads to increase in serum levels of prolactin hormone.

Idiopathic hyperprolactinemia

This diagnosis is made when no specific cause for the elevated serum prolactin levels can be identified.

CHRONIC KIDNEY DISEASE

Chronic Kidney Disease [CKD] is defined using following criteria

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by *either*: • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage

CKD is classified in to five stages:

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

CLINICAL MANIFESTATIONS:

Uremia leads to disturbances in the function of every organ system.Various clinical and laboratory manifestation of CKD is as follows,

With the exception of hypertension, there are usually few clinical manifestations during CKD stages 1and 2 [GFR >60 ml/min], the presence of proteinuria or haematuria being dependent on the underlying cause of kidney disease. Other complications tend to develop progressively as the GFR declines below30 ml/min.

Hypertension

- Between 50% to 70% of individuals with CKD stagesIII to V have hypertension [>140/90 mmHg].

Dyslipidemias

Patients with CKD stage III & more develop a disturbance of lipoprotein metabolism.There occurs accumulation of partially metabolized VLDL particles.There occurs a disturbance in the maturation of high – density lipoprotein.Blood tests typically show hypertriglyceridemia with low HDL cholesterol concentrations.Total cholesterol levels are normal. LDL – cholesterol levels are normal. But both may be low in the patients with concomitant inflammation and malnutrition.

Anemia

- Anemia is seen in CKD stages III to V.

Causes for anemia in CKD are as follows;

- Deficiency of erythropoietin.
- Reduced availability of serum iron.
- Chronic inflammation.

Bone and Mineral Metabolism

Hyperphosphatemia, together with a deficiency of the 1, 25 –dihydroxy vitamin D3 contributes to the development of renal bone disease.These biochemical and endocrine abnormalities may be evident in patients with CKD stage III and are well established in those who reach ESRD.Even though they rarely lead to symptomatic bone disease until patients have been on dialysis for several years.

Metabolic acidosis

The metabolic acidosis associated with chronic kidney disease is caused by following factors

- Failure of hydrogen ion excretion.
- This is further compounded by bicarbonate loss, particularly in interstitial kidney diseases.

Malnutrition

Malnutrition is common among patients on dialysis.Malnutrition may occur in those with CKD stages IV to V.Malnutrition is associated with increased risk for death.Causes for malnutrition include anorexia, acidosis, insulin resistance, inflammation, and urinary protein loss.

Sodium and Water retention

Sodium handling by the kidney is altered in CKD although plasma sodium concentrations are generally within normal range.Most patients with chronic kidney disease develop expansion of extracellular volume.They also tend to have retention of sodium in the long run.

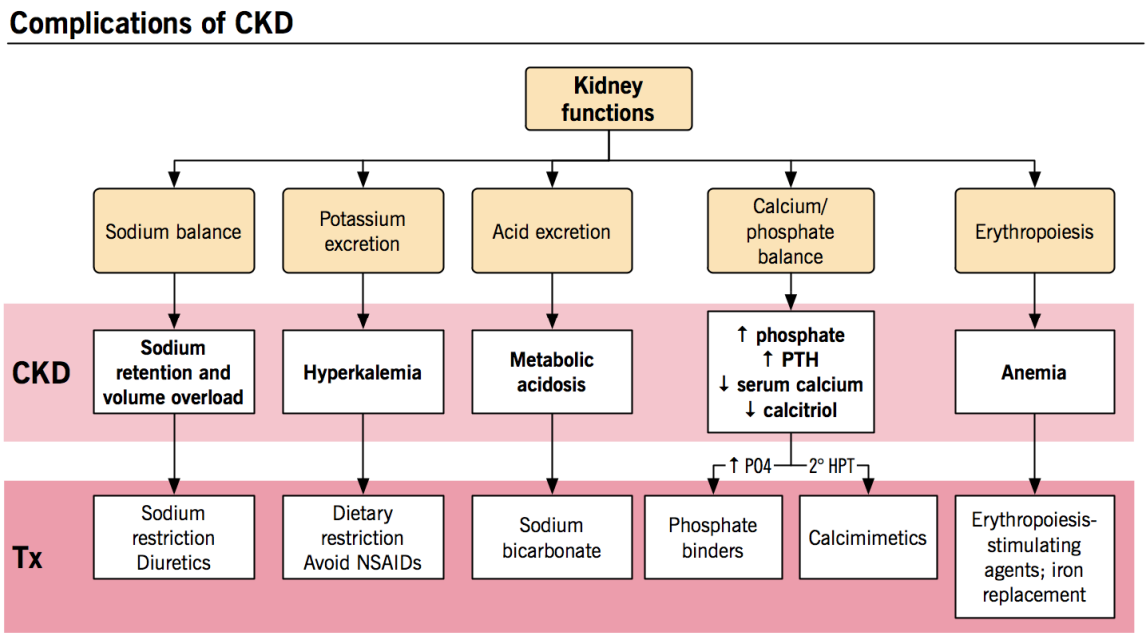
Potassium

- Hyperkalemia is a common finding in patients with CKD stages IV - V.

Immunity

Infections contribute significantly to mortality in patients with CKD stage V receiving dialysis next only to cardiovascular diseases.This is explained in part by the invasive procedures required for the delivery of RRT. CKD is a state of chronic immunosuppression with defects in both cellular and humoral immunity.The clinical manifestations of these

immune defects include increased susceptibility to bacterial infection particularly staphylococcal infection.CKD patients are at increased risk for reactivation of tuberculosis [Typically with a negative tuberculin skin test].CKD patients show inability to eliminate hepatitis B and C virus following infections.CKD patients should be immunized against hepatitis B as early as possible in an effort to maximize the chance for seroconversion.



ENDOCRINE ABNORMALITIES IN CKD

Type of defect	Example
Abnormalities of hormone production	
Reduced hormone production by the kidney	Erythropoietin, $1,25(OH)_2D_3$
Reduced hormone production in endocrine organs	Testosterone, estrogen
Abnormal secretion pattern (pulsatility; circadian rhythm)	PTH, GH, LH
Reactive hypersecretion of hormone to reestablish homeostasis	Erythropoietin, PTH, FGF 23
Inappropriate hypersecretion due to disturbed feedback	LH, prolactin, corticotropin
Abnormalities of hormone catabolism	
Decreased metabolic clearance	PTH, insulin, gastrin, leptin, adiponectin
Abnormalities of hormone action	
Disturbed activation of prohormones	Proinsulin, thyroxin (T_4)
Increased isoforms with potentially less bioactivity (due to posttranscriptional modifications)	LH
Increased hormone-binding proteins in plasma reducing availability of free hormone	IGF
Decreased hormone-binding proteins increasing availability of free hormone	Leptin
Changed receptor number, structure, modification	Vitamin D receptor
Disturbed postreceptor cellular signaling	Insulin, GH

Thyroid Hormones

Total plasma thyroxine [T4] levels may be low, with an associated increase in reverse triiodothyronine [T3] as a result of impaired conversion of T3 to T4.Loss of thyroid binding globulin may further lower total circulating T4 concentrations. However, patients do not become clinically hypothyroid, and measurement of thyroid – stimulating hormone remains a reliable diagnostic test for hypothyroidism in CKD.

Growth Hormone

Plasma growth hormone levels may be elevated in patients with CKD stage V because of delayed clearance and alterations in hypothalamic – pituitary control. In children, growth retardation may result and can be corrected by treatment with exogenous recombinant growth hormone given in supraphysiologic doses.

Insulin

Decreased clearance of insulin is balanced by increased peripheral resistance to the effects of the hormone. As a result, there are usually no clinical manifestations, and patients are not particularly prone to hypoglycemia. However in diabetic patients, these effects may lead to a

falling requirement for insulin as kidney function deteriorates a trend that may be reversed by the initiation of dialysis.

SEX HORMONES

Males

Prolactin levels are elevated in CKD stage V and may contribute to gynaecomastia and sexual dysfunction[1,2,3&68] .Testosterone levels are often low – normal, and gonadotropins may be raised, implying testicular failure[82]. This is accompanied by poor spermatogenesis, leading to low sperm counts and reduced fertility .It is appropriate to prescribe androgen replacement treatment if testosterone levels are unequivocally low, not least because this may help to prevent osteoporosis. Perhaps the most important and sexual problem in males is erectile dysfunction , although this is more likely to result from neurologic ,psychological and vascular abnormalities than endocrine disturbances and may respond to phosphodiesterase type 5 inhibitors such as sildenafil citrate.

Females

The pituitary – ovary axis may be disturbed by CKD stages 4 to 5[83].In female chronic kidney disease patients levels of Luteinizing hormone are increased.Menstrual Cycles in female CKD patients are therefore often anovulatory and may be irregular, or there may be amenorrhoea.Serum

levels of hormone prolactin are raised in female CKD patients.Female CKD patients may present with infertility.Rarely women receiving dialysis conceive and very rarely carry to term.

HYPERPROLACTINEMIA IN CHRONIC KIDNEY DISEASE

Males

About 40 -70 percent of Male CKD patients have an elevated Serum prolactin level[74] and the biological activity of this hormone is also increased[4]. As renal failure progresses , elevation of prolactin levels seems to correlate with serum creatinine .The normal circadian rhythm of prolactin secretion is disturbed in that the characteristic sleep – induced secretory bursts are not found , although episodic secretion occurs during daytime[75].

Hyperprolactinemia in uremic patients cannot be explained by slightly diminished prolactin clearance. A primary mechanism seems to be inadequate dopaminergic inhibition of prolactin release from the pituitary lactotrophs[1]. Other authors reported that basal and stimulated prolactin concentrations became subnormal after the long – term administration of dopaminergic agonists such as bromocriptine, suggesting that prolactin secretion in uremic patients can be suppressed at least by chronic dopaminergic stimulation. Characteristic stimuli such as thyrotropin –

releasing hormone, chlorpromazine, metoclopramide, and arginine or insulin – induced hypoglycemia result in blunted prolactin response in dialyzed patients.

In uremic men, hyperprolactinemia is associated with sexual dysfunction, loss of libido, impaired erection potency, and infertility[5,67]. It is not known whether the exact mechanism of this disturbed sexual function results from a gonadal effect of prolactin or from a hypothalamic hypophyseal effect. In uremic patients, the hypothalamic LHRH release is apparently suppressed, and high prolactin levels may be implicated in this abnormality. However the diminished peripheral clearance of LH prevents association of hyperprolactinemia with low LH levels.

Females

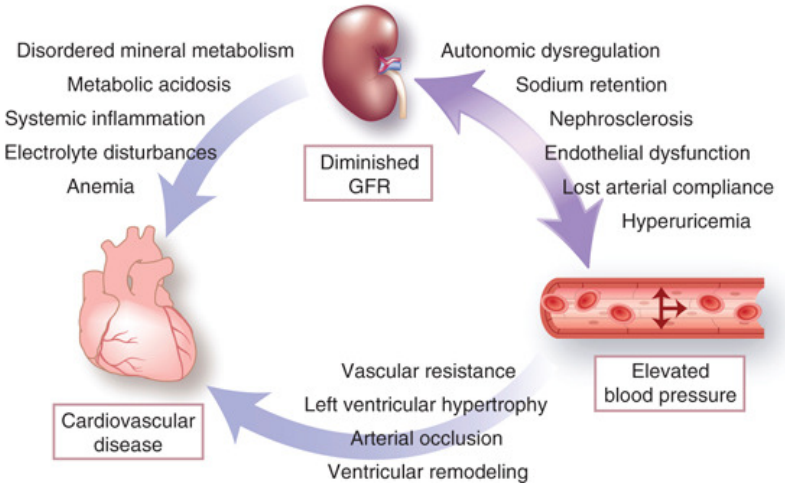
Hyperprolactinemia is common among female CKD patients[76]. Compared to healthy controls, the increase of serum prolactin is blunted after thyrotropin – releasing hormone stimulation. Hyperprolactinemia is a well – known cause of galactorrhoea and gonadal disturbance with menstrual irregularities, commonly amenorrhoea, in uremic patients. Amenorrhoea is found in patients with regular menstruation. Other menstrual irregularities, including anovulatory cycles or oligomenorrhoea, are more frequent in hyperprolactinemic patients than galactorrhoea, which is the classical symptom of hyperprolactinemia.

PROLACTIN	
WOMEN	**MEN**
Loss of libido	Loss of libido
Mood changes / depression	Mood changes/depression
Hostility, anxiety	Impotence
Headache	Headache
Menopausal symptoms, even when estrogen is sufficient	Infertility
Signs of increased testosterone levels	Decreased testosterone levels
Weight gain	Weight gain
Intercourse may become painful because of vaginal dryness	Peripheral vision problems
Infertility, irregular menstruation	Gynecomastia (growing breasts)
Peripheral vision problems	

CORONARY ARTERY HEART DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Nearly one half of patients with chronic kidney disease have coronary artery heart disease among them. Among patients with chronic kidney disease silent coronary artery heart disease is also common. Coronary Artery Heart Disease significantly contributes to morbidity and mortality in patients with chronic kidney disease.

ISCHEMIC HEART DISEASE



ATHEROMATOUS ISCHEMIC HEART DISEASE

In humans basal myocardial perfusion tends to remain constant .This is maintained irrespective of degree of stenosis of coronary arteries. When there is a demand for increased perfusion, a progressive relative decrease in perfusion occurs after the degree of stenosis is greater than 40 % or greater, and perfusion cannot increase above basal conditions when the stenosis is greater than 80% or greater. Therefore, stenosis progressively exhausts the coronary vasodilator reserve .The predisposing conditions for CKD as well as the CKD itself contributes to the atherosclerotic processes. The metabolic disturbances and inflammatory processes in CKD facilitate the atherosclerotic process. There is infiltration of arterial wall with lipid laden macrophages. These are called as foam cells. There is proliferation of fibroblast cells in the arterial wall. There is proliferation of smooth muscle cells as well. This results in proliferation of atherosclerotic plaque .This atherosclerotic plaque facilitates clot formation

Coronary Artery Disease, characterized by the critical stenosis of the major coronary arteries is highly prevalent in the CKD patients.

Systemic hypertension is one of the major predisposing factors for the atherosclerotic process. Systemic hypertension creates stress to the vascular tree. The stress created by systemic hypertension is of two types. One is the tensile stress. Another one is shear stress. Both types of stress contribute to atherosclerotic process. These stress forces act on the vascular tree mainly on the bifurcations. They also act on the orifices of vasculature. This leads to facilitation of atherosclerotic process. This leads to activation of endothelial cells .This subsequently results in secretion of several growth factors. Subsequent effects include alterations in cytokine migration, cellular apoptosis, and extracellular matrix synthesis. Chronic kidney disease leads to activation of endothelial cells in long term.

In addition to endothelial injury and activation, the vascular pathology of chronic uremia includes autocrine and endocrine sequelae from a diverse range of seemingly unrelated factors. These include Dyslipidemias, Altered platlet function, free radical mediated injury because of stress created by oxygen derived free radicals, Decreased whole body antioxidant content level, increased serum levels of homocysteine, impaired glucose tolerance, occurrence of a state of chronic inflammation due to imbalance between various cytokines.

Two factors have received particular attention recently in regard to their contribution to the development of atheroma in CKD: inflammation and vascular calcification.

Inflammation in general, and C-reactive protein in specifically, may contribute directly to the pathogenesis of atherosclerosis and its complications both in general and in patients with CKD.CRP has been shown to bind to damaged cells, promoting activation of compliment system.C Reactive protein binds to atherogenic lipoproteins a potent stimulator of tissue factor by monocytes.Epidemiologic studies support its pathogenic role as a cardiovascular risk factor in the general community. In CKD the sources of elevation in CRP is uncertain. Potential sources include back filtration of endotoxin during dialysis, type of vascular access, unrecognized infection, and bioincompatibility of peritoneal dialysate. CRP levels have been shown to have a powerful predictive value for mortality in both haemodialysis and peritoneal dialysis recipients and to be an independent predictor of the number of atherosclerotic plaques and of intima – media thickness in carotid arteries of haemodialysis patients respectively.

In one study, coronary atherosclerotic plaque morphology in patients with CKD was distinguished most readily by composition rather than by size or number.

In patients with chronic kidney disease Atherosclerotic plaques are characterized by more extensive deposition of calcium ions. This may be a contributory factor for the increased rate of complications seen in patients with coronary artery disease. Although coronary artery calcification is predictive of subsequent coronary events in the general population, its clinical significance in patients with CKD is unknown. It is possible that the more generalized arterial calcification observed in dialysis patients is not predictive of atherosclerotic coronary events, but rather is a marker for arteriosclerosis and diminished vascular compliance and a risk factor for LV hypertrophy.

NON ATHEROMATOUS ISCHEMIC HEART DISEASE

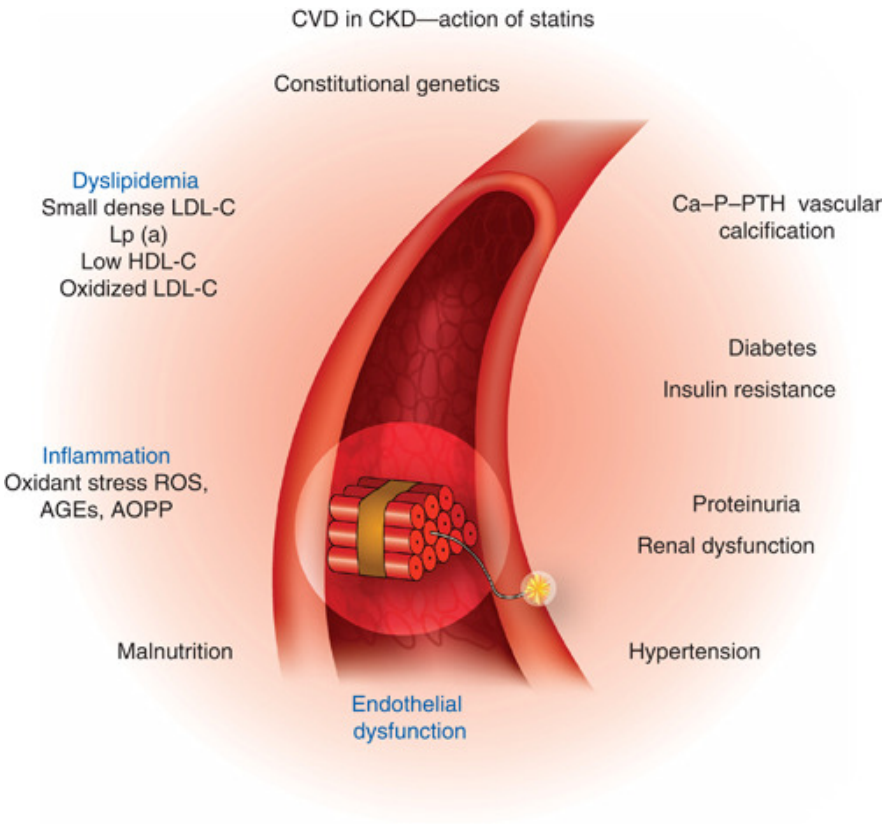
About 25% of dialysis patients with ischemic symptoms do not have critical CAD.A significant percentage of predialysis and transplantation patients are similarly affected. It is likely that these symptoms result from micro vascular disease and the underlying cardiomyopathy. In this group of patients there is reduction in the maximal dilatory capacity of coronary vessels. In addition there is alteration in the oxygen delivery pattern to the myocardium. Together these contribute to the ischemia in this patient group.

In patients with Chronic Kidney Disease presence of Left Ventricular Hypertrophy predisposes these patients to ischemia even in the absence of demonstrable atherosclerosis in their coronary vasculature. LV hypertrophy is primarily a response to increased tensile stress. This requires an overall increase in myocardial energy .This increases the demand for oxygen by the myocardium. This increased demand for oxygen by the myocardium necessitates dilatation of coronary vessels. If atherosclerotic processes have affected the coronary vessels this dilatation induced increased flow may not be sufficient to meet the increased demand by the myocardium for oxygen. Atherosclerosis of the small intramyocardial coronary vasculature is partly responsible for the reduction in subendocardial perfusion.

In patients with chronic kidney disease there is hypertrophy of left ventricle myocardium. In this group of patients there is hypertrophy of smooth muscle cells situated in the wall of small vessels of coronary vasculature. This also predisposes this group of patients for ischemia. In patients with chronic kidney disease compliance of coronary arteries are reduced. This also predisposes this group of patients for myocardial ischemia there is abnormal balance in the high energy phosphate compounds in patients with chronic kidney disease. This also contributes to ischemic symptoms in them. Secondary hyperparathyroidism which is

seen in patients with chronic kidney disease is also a contributory factor for ischemia.

RISK FACTORS



Age

Incidence of chronic kidney disease increases with age which is also the case for coronary artery heart disease. The risk for death increases by 3% per year of age.

Gender

The incidence of coronary artery heart disease is more common among male patients with chronic kidney disease than female patients. When compared to general female population female patients with chronic kidney disease are more prone to develop coronary artery heart disease

Smoking

Smoking is found to increase the risk of coronary artery heart disease among CKD patients.

Diabetes Mellitus

Those chronic kidney disease patients with diabetes are at more risk of developing coronary artery heart disease.Those chronic kidney disease patients with diabetes also have other risk factors for coronary artery disease like dyslipidemia , hypertension , signs of inflammation , increased oxidative stress , & wasting.

Hypertension

Presence of hypertension predicts mortality in patients with CKD.The following factors predict the risk of coronary artery heart disease in patients with chronic kidney disease.

Isolated systolic hypertension

Increased pulse pressure.

Dyslipidemia

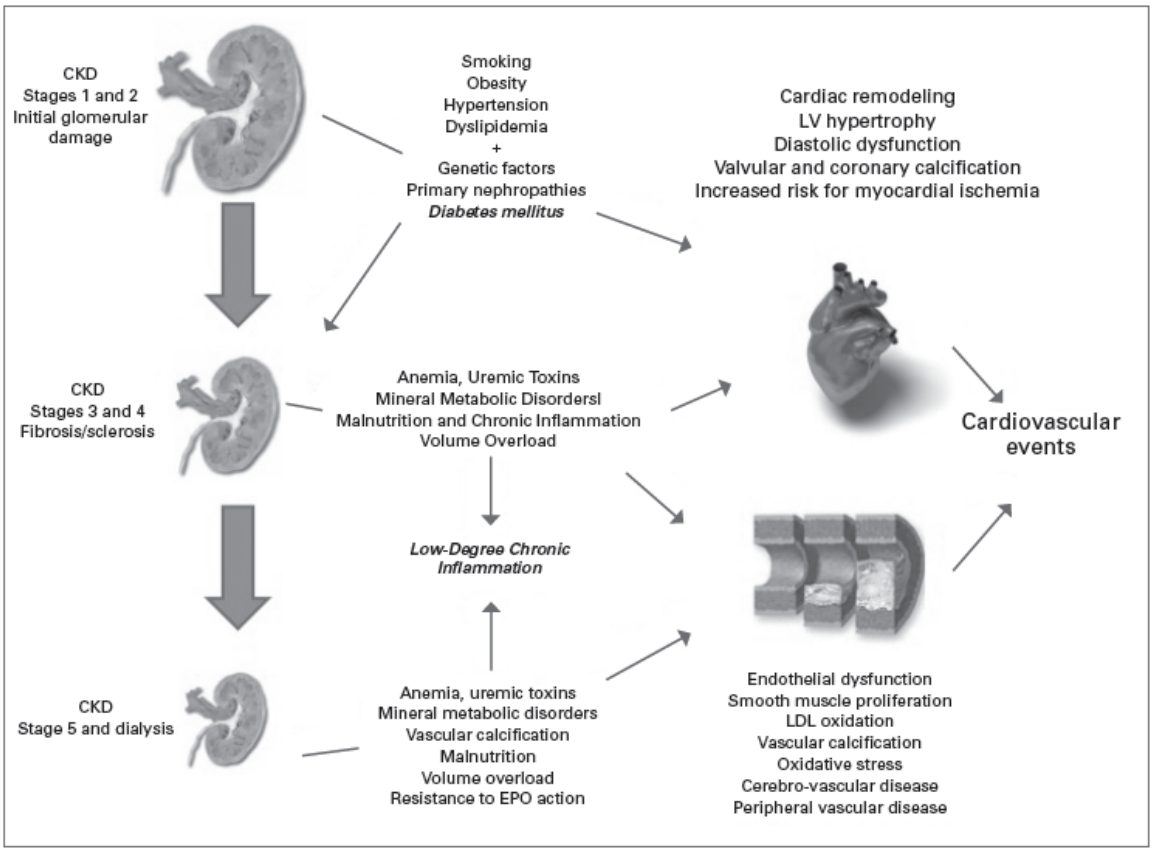
In the CKD population, the relationship among hypercholesterolemia, CVD, and mortality is weak.

Insulin resistance

Chronic kidney disease patients with metabolic syndrome exhibit varying level of insulin resistance. But the relationship between this insulin resistance and risk of coronary artery disease is currently unclear.

Nontraditional Risk factors & Risk factors specific to chronic kidney disease

Figure 1. Pathophysiology of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD)



In the initial stages of CKD, the traditional risk factors for CVD act as triggers not only for initiating the deleterious modifications in the cardiovascular system, but also as promoters of CKD progression. In intermediary stages of the disease, the typical CKD phenomena involved in the pathogenesis of CVD, such as anemia, mineral metabolic disorders, and systemic inflammation begin to install. In CKD end stages and dialysis phase, traditional risk factors, those inherent to uremia, and new specific factors related to the ongoing dialysis modality, work jointly. Systemic low-degree chronic inflammation plays a central role in pathophysiology. Several myocardial alterations, especially those associated with fibrosis and vascular calcifications, occur, justifying innumerous events of sudden death (due to cardiac arrhythmias) and congestive heart failure. Atherosclerotic damage in medium and large-caliber arteries account for cerebro-vascular accident, peripheral vascular disease, and abdominal aorta aneurysm.

Chronic kidney Disease itself is now considered an independent risk factor for occurrence of coronary artery heart disease .The following factors are attributed for this increased risk of coronary artery heart disease among patients with chronic kidney disease.

Oxidative stress

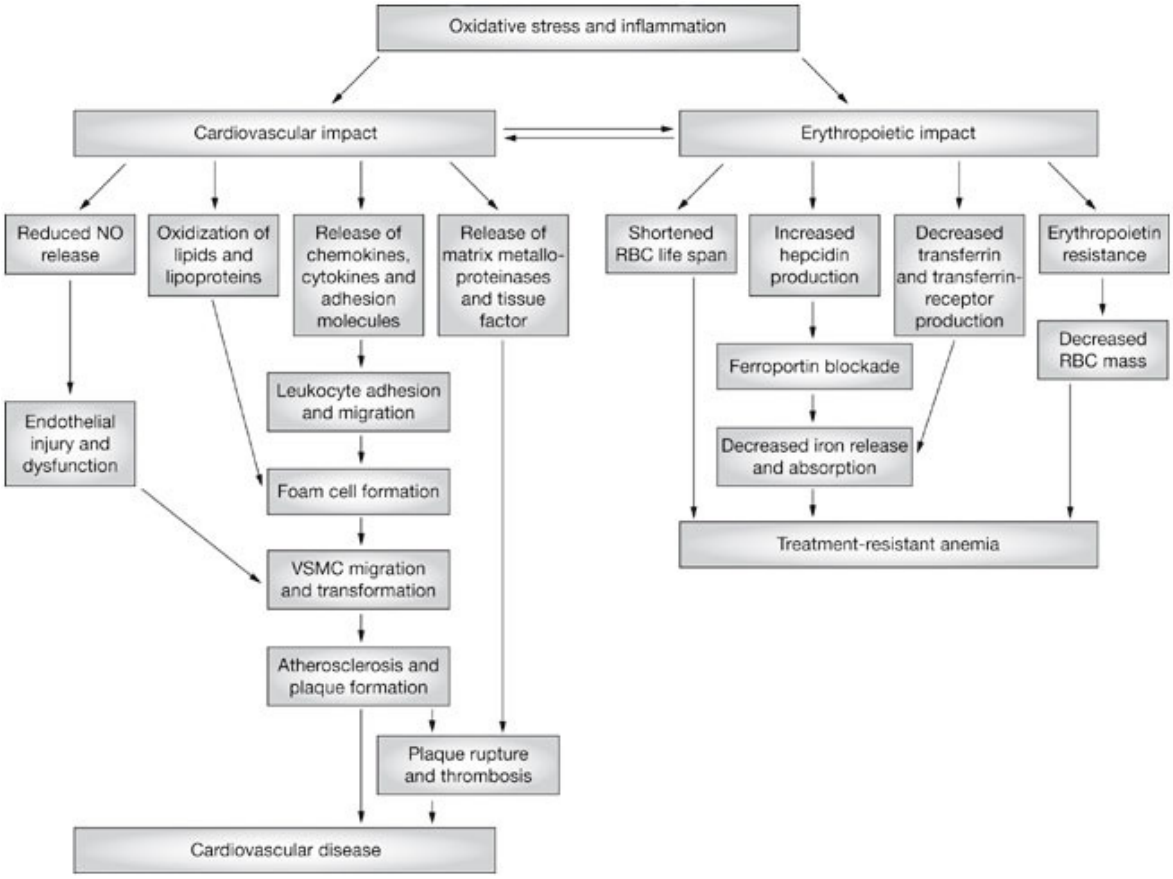
Inflammation

Vascular calcification

Advanced glycation end products

In addition several other uremic retention solutes may have pro atherogenic properties. Finally healthy kidneys produce substances that inhibit CVD and atherogenesis, such as renalase, a soluble monoamine oxidase that regulates cardiac function and blood pressure. In ESRD, very low plasma concentrations of this putative inhibitor of the sympathetic nervous system may contribute to sympathetic overactivity.

Oxidative Stress



Increased oxidative stress, that is unbalanced surplus of free radicals is associated with increased risk for atherosclerosis and increases the risk for coronary artery heart disease, chronic kidney disease patients are characterized by decreased anti oxidant activity and increased prooxidant activity inside the body. Because of poor appetite and nutritional status these chronic kidney disease patients also suffer from deficiency of antioxidants.

Inflammation

Several studies have demonstrated that chronic kidney disease patients are in a state of chronic inflammation. This is evidenced by increased level of inflammatory bio markers such as C - reactive protein in them. These inflammatory biomarkers are associated with atherogenic properties and facilitate atherosclerotic process.

Endothelial dysfunction

Endothelial dysfunction [as evidenced by impaired endothelium – dependent vasodilatation] is a prominent feature of CKD .The reasons for this include a state of chronic inflammation , oxygen dependent free radical mediated injury , increased serum levels of homocysteine, impaired glucose tolerance , abnormal lipid metabolism and systemic hypertension.

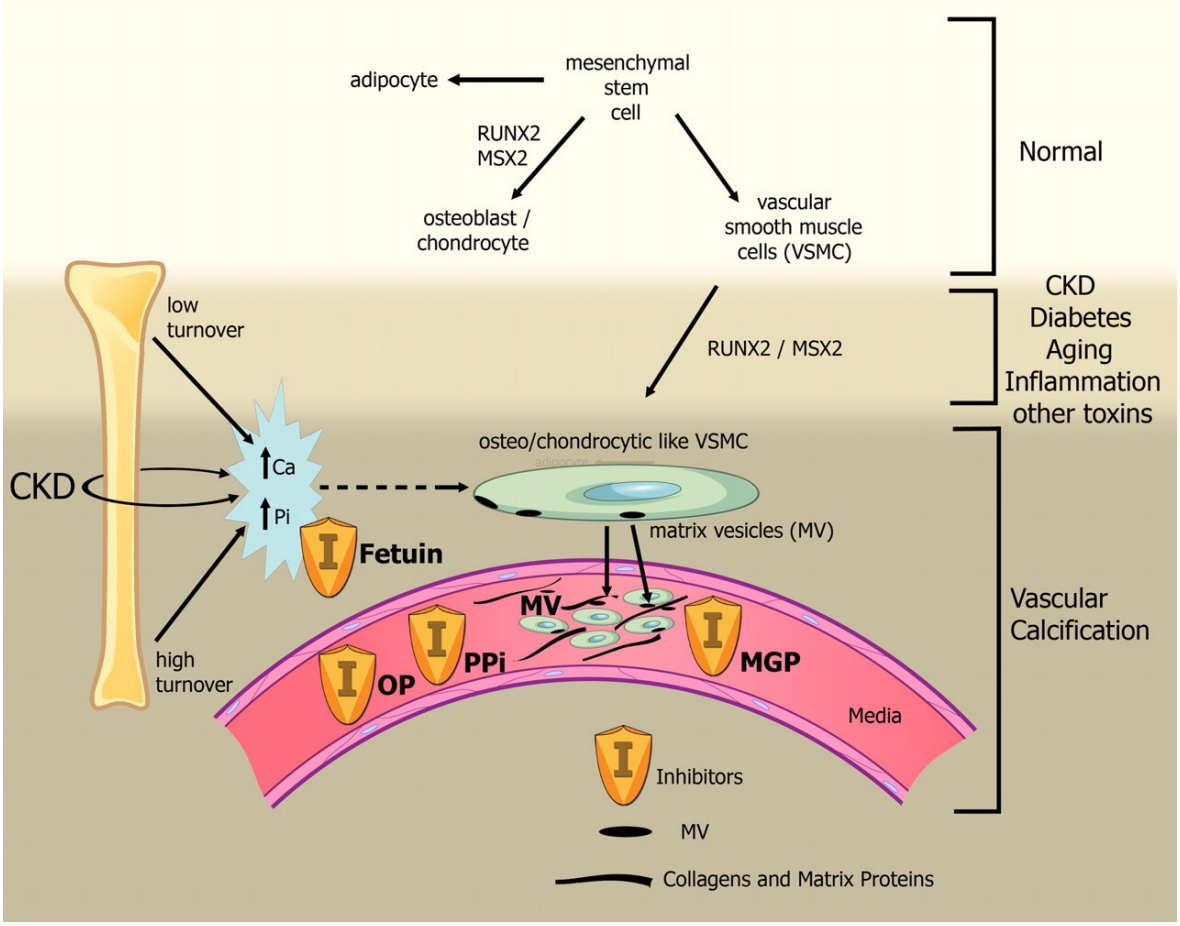
Anemia

Anemia in patients with chronic kidney disease leads to Left Ventricular Hypertrophy and over a long term leads to dilatation of left ventricle.

Secondary Hyperparathyroidism and Mineral Metabolism

Disturbance of calcium and phosphate metabolism start as early as CKD stage 3 and are potent triggers of accelerated calcifying atherosclerosis and arteriosclerosis.

Cardiovascular Calcification



Calcification may affect the media of arterial tree, atherosclerotic plaques, myocardium, and heart valves. Medial calcification cause arterial stiffness and consequently increased pulse pressure. In patients with chronic kidney disease calcification of coronary vasculature is very common. This calcification of coronary vasculature predicts the long term risk of coronary artery heart disease among patients with chronic kidney disease.

Advanced Glycation End products

Advanced Glycation End products accumulate in CKD and may contribute to accelerated atherosclerosis and increases the risk of coronary artery heart disease among them.

Hyperhomocysteinemia

The prevalence of hyperhomocysteinemia in CKD stage 5 exceeds 90 %.However the relationship between high homocysteine serum levels and CVD in CKD patients has been reported variably. However some studies even noted paradoxically lower levels of Homocysteine in uremic CVD patients.

HYPERPROLACTINEMIA IN CKD PATIENTS & RISK OF CAHD

Chronic kidney disease is associated with a state of chronic inflammation. This state of chronic inflammation predisposes these patients to increased risk of atherosclerosis and coronary artery heart disease. Recent studies are showing that Prolactin may have a role in the process of atheroscelrosis.Hyperprolactinemia is found in patients with essential hypertension[7]. Hyperprolactinemia is found in patients during the acute phase of coronary syndrome[11]. During the ischemic stroke episodes also hyperprolactinemia is found[12,13]. Increased serum levels of prolactin are

found in men with erectile dysfunction. This increase in serum prolactin level positively predicted increased cardiovascular risk among them[17]. Increased serum levels of prolactin hormone found in patients with preeclampsia and they play a causative role in the heart failure that accompanies post partum cardiomyopathy[14,15,16]. In some recent studies Prolactin receptors were found to be abundantly present atherosclerotic plaques[18,19] .That too these receptors were found to be abundantly present in the macrophages at sites of most prominent inflammation.

So Hyperprolactinemia in patients with CKD may be a contributing factor for the enhanced inflammation seen in CKD patients. Hyperprolactinemia in CKD patients may contribute to endothelial dysfunction [4].Hyperprolactinemia in CKD may contribute to increased atherogenesis[4] .It may be a contributing factor for vascular derangements seen in CKD patients. Hyperprolactinemia may be a causative factor for the worst cardio vascular outcome seen in patients with CKD[81].

MATERIALS AND METHODS

The study was conducted in 50 patients with chronic kidney disease .All of the patients were on Conservative line of treatment.

The study was conducted in patients admitted in Thanjavur medical college hospital between January 2014 to August 2014.

The patients who fulfill the criteria for CKD and who were on Conservative line of treatment were taken in to study. The patients were evaluated with ECG and ECHO for presence of Coronary Artery Heart Disease and fasting serum prolactin level was measured in them to assess the presence of hyperprolactinemia.

Criteria for Chronic Kidney Disease:

1. Patients with established Chronic Kidney Disease irrespective of etiology.
2. Symptoms of uremia for 3 months or more.
3. Elevated blood urea, serum creatinine and decreased creatinine clearance.

4. Ultrasound evidence for Chronic Kidney Disease:

   A] Bilateral contracted kidney – size less than 8 cm in male and less than 7cm in females.

   B] Poor cortico medullary differentiation.

   C] Type II or III Renal Parenchymal changes.

5. Following group of patients were excluded from my study:

   A] Known patients of hypothyroidism.

   B] Known patients of chronic liver disease.

   C] Known patients with seizure disorder.

   D] Those who are pregnant.

   E] Patients with Prolactinomas, Acromegaly & Cushing‘s disease.

   F] Patients with Craniopharyngioma, Meningiomas, Sarcoidosis.

   G] Patients with chest wall lesions /surgeries, Spinal cord lesions.

   H] Patients with adrenal insufficiency.

   I] those patients on following medications:

Phenothiazines. Butyrophenones. Chlorpromazine. Sulpiride. Metoclopramide. Antiemetic agents. Major tranquilizers.
Tricyclic anti depressants. Mono Amine Oxidase inhibitors. Selective Serotonin reuptake inhibitors.
Opiod abuse. Cocaine abuse.
Alpha Methyl Dopa. ACE inhibitors: Enlapril. Reserpine.
Verapamil
Protease inhibitors.
H 2Blockers

Detailed clinical history and examination were undertaken in all patients. Height and weight and Blood pressure of all patients were recorded.

The following investigations were performed in them.

- Complete Blood Count
- Peripheral Smear Study
- ESR
- Blood sugar fasting, post prandial.
- HbA1C
- Blood urea
- Serum Creatinine
- Creatinine Clearence
- Serum Electrolytes
- Liver Function Test
- Lipid profile
- Hbs Ag
- HCV
- HIV
- Urine for albumin, sugar and deposits.
- Chest – X ray.
- ECG
- ECHO
- USG abdomen
- Fasting Serum Prolactin level

After selecting the patients, about 5 ml of blood sample is collected in a non – heparinized bottle and sent for serum prolactin measurement.

Quantitative determination of Serum Prolactin was done by Fully Automated Bidirectionally Interfaced Chemi Luminescent Immuno Assay.

The Reference range for serum Prolactin includes:

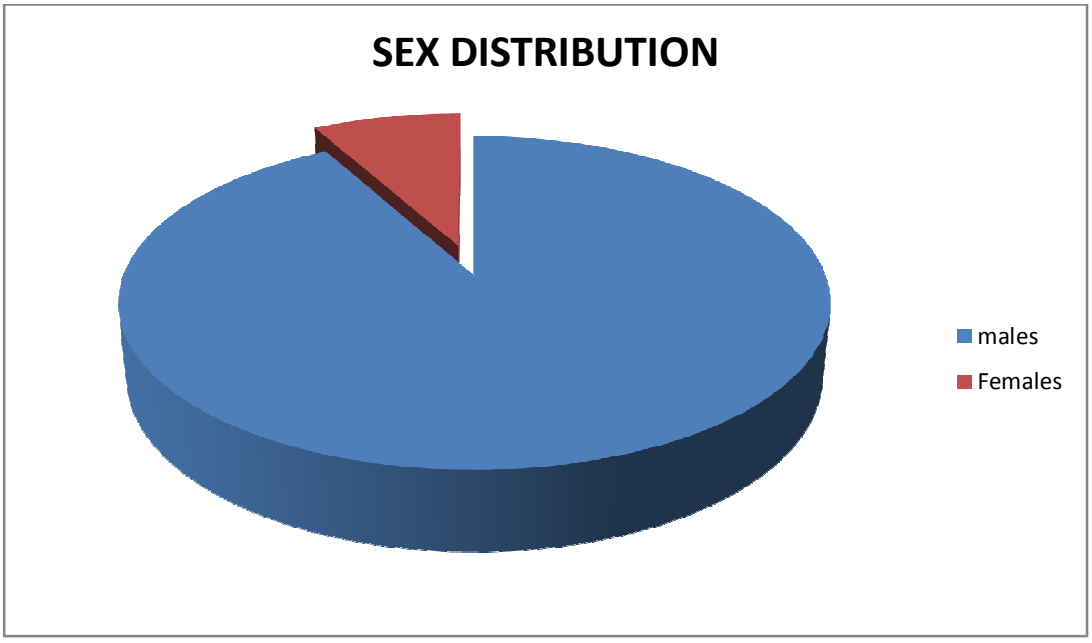
Normally menstruating females	: 2.8-29.2 ng/ml.
Pregnant women	: 9.7-208.5 ng/ml.
Post menopausal women	: 1.8-20.3 ng/ml.
Men	: 2.1-17.7 ng/ml.

RESULTS AND OBSERVATIONS

50 Patients with Chronic Kidney Disease who were on conservative line of treatment were studied.

Among 50 patients 46 patients were male patients and 4 patients were female patients.

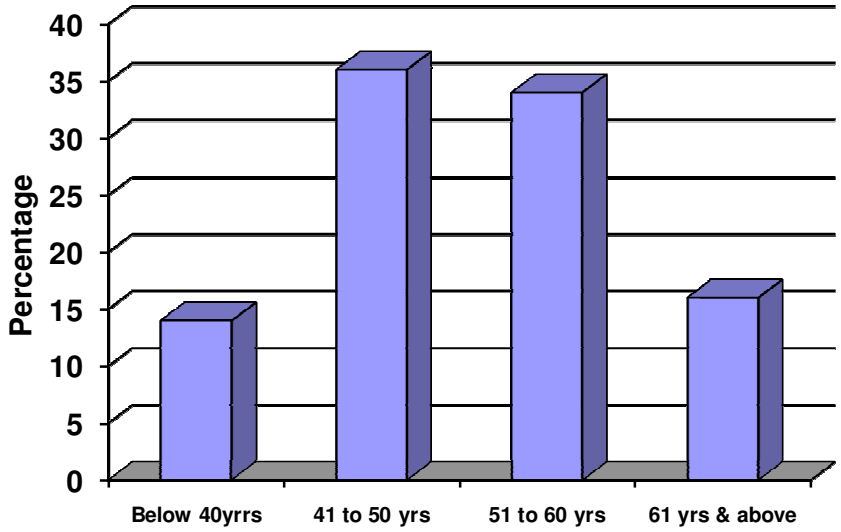
Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Male	46	92.0
Female	4	8.0



Age distribution

The patients of chronic kidney disease, in my study were between 29 years to 70 years. Among 50 patients with chronic kidney disease , 7 patients were below 40 years of age , 18 patients were in the age group of 41-50 years, 17 patients were in the age group of 51-60 years , 8 patients were 61 years and above.

Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Below 40yrs	7	14.0
41 to 50yrs	18	36.0
51 to 60yrs	17	34.0
61yrs & above	8	16.0

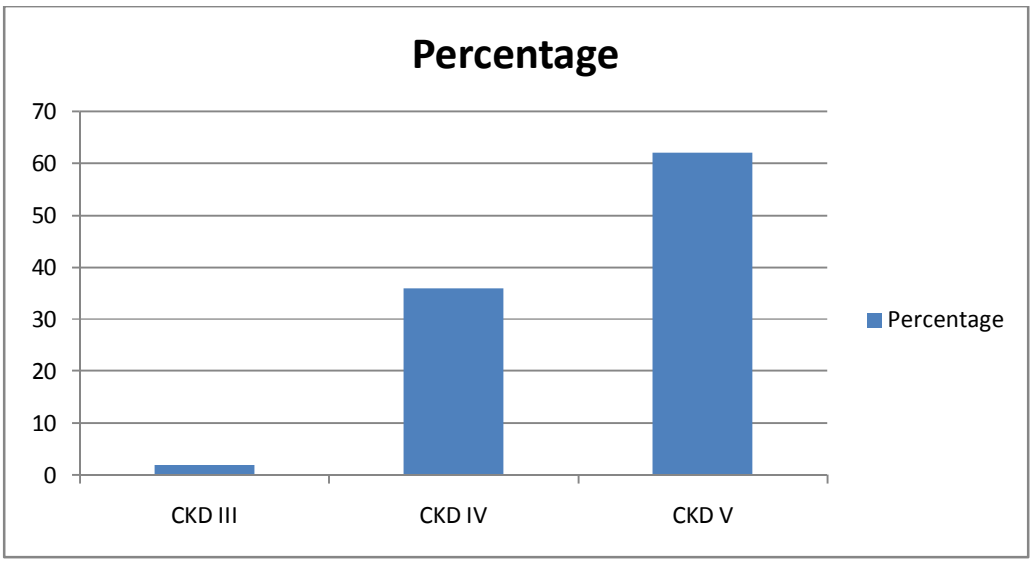


Observation regarding Chronic Kidney Disease in this study

The duration of Chronic Kidney Disease in this study varied from 6 months to 8 years.

The creatinine clearance varied from 4.77 – 46.0.Among the 50 CKD patients 31 had creatinine clearance <15 ml/min, 18 patients had creatinine clearance 15-30 ml/min, 1 patient had creatinine clearance in the range of 30-60ml/min.

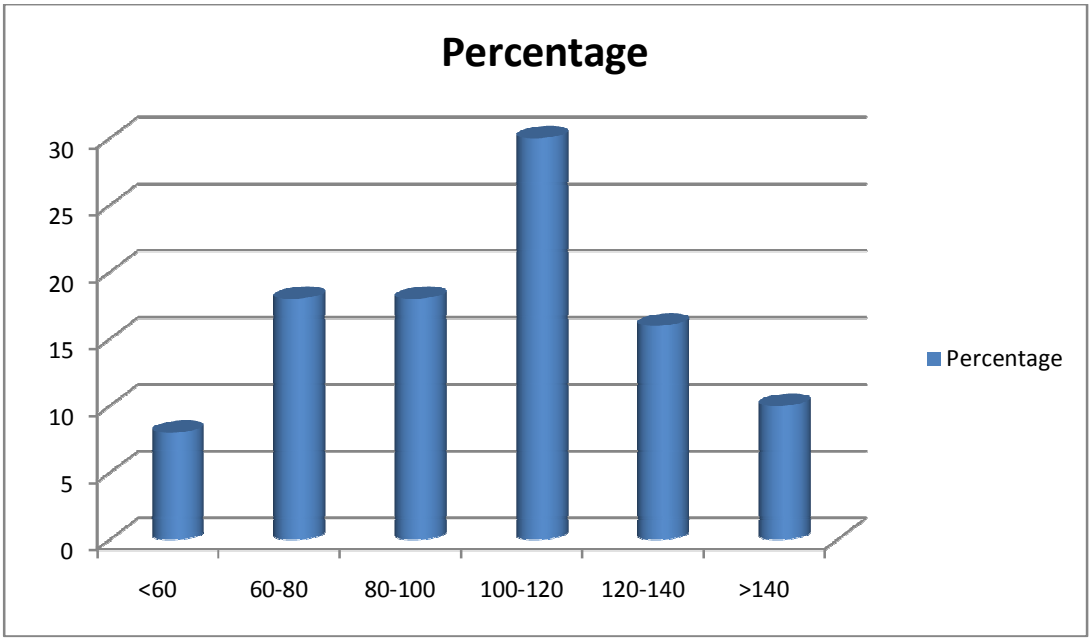
Creatinine clearance ml/min	CKD Stage	No. of .Respondents	Percentage
30-60	III	1	2
15-30	IV	18	36
<15	V	31	62



Blood Urea level distribution

Among the 50 patients with CKD Blood urea values varied from 45 mg/dl to 170 mg/dl.

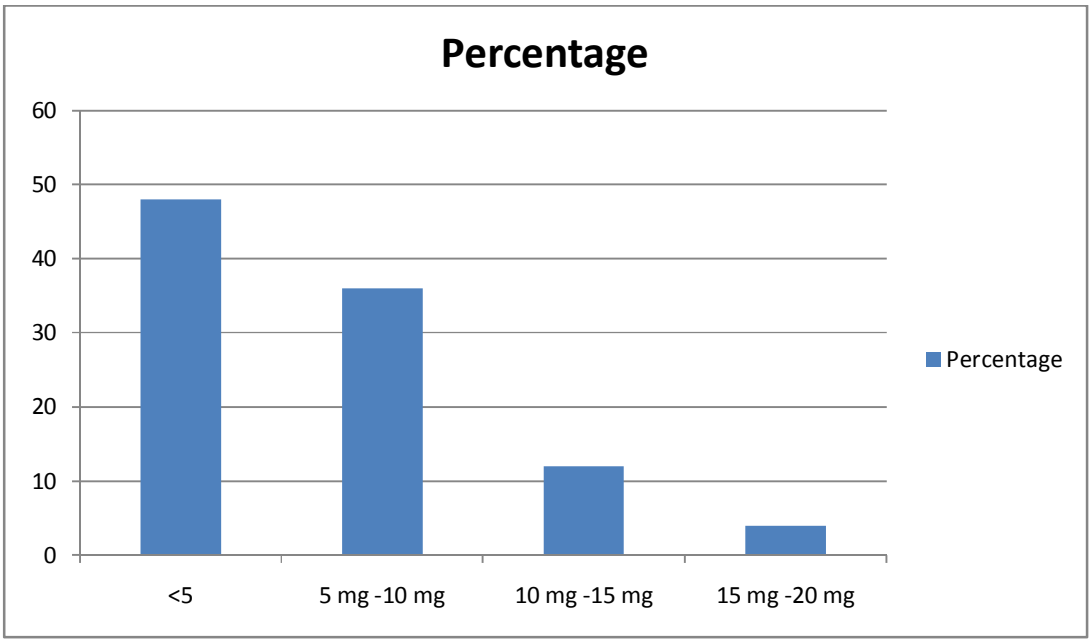
Blood Urea[mg/dl]	No.of.Patients	Percentage
<60	4	8
60-80	9	18
80-100	9	18
100-120	15	30
120-140	8	16
>140	5	10



Serum creatinine values

Among the CKD patients serum creatinine values varied between 1.5 mg/dl to 18.4 mg/dl.

S.Creatinine level	No. of .Patients	Percentage
<5	24	48
5-10	18	36
10-15	6	12
15-20	2	4



Systemic Hypertension

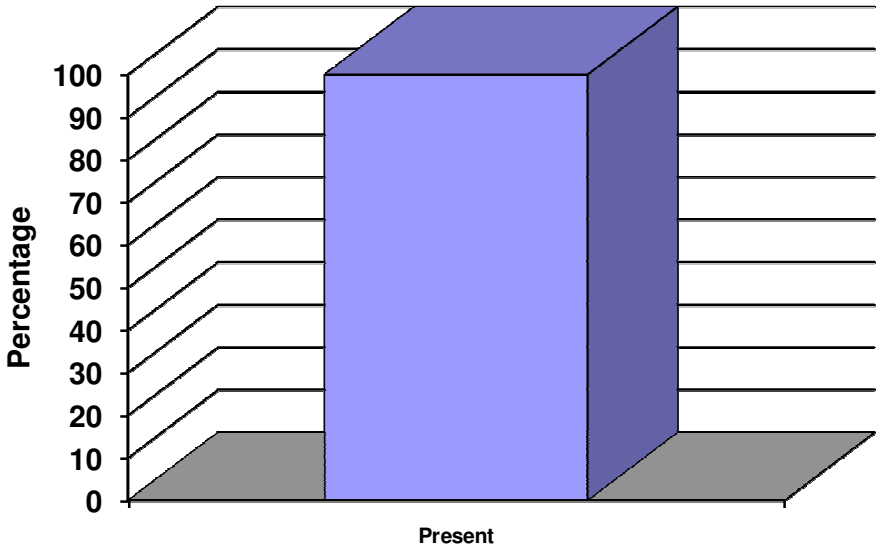
Classification of systemic hypertension

Based on the JNC 7 classification

CATEGORY	SYSTOLIC BLOOD PRESSURE mmHg	DIASTOLIC BLOOD PRESSURE mmHg
Normal	<120	<80
Prehypertension	120-139	80-89
Stage I	140-159	90-99
Stage II	>160	>100

In the 50 chronic kidney disease patients studied all of them were found to be patients of systemic hypertension.

Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Present	50	100.0



Type 2 Diabetes Mellitus

Patients were diagnosed to have diabetes based on the following criteria:

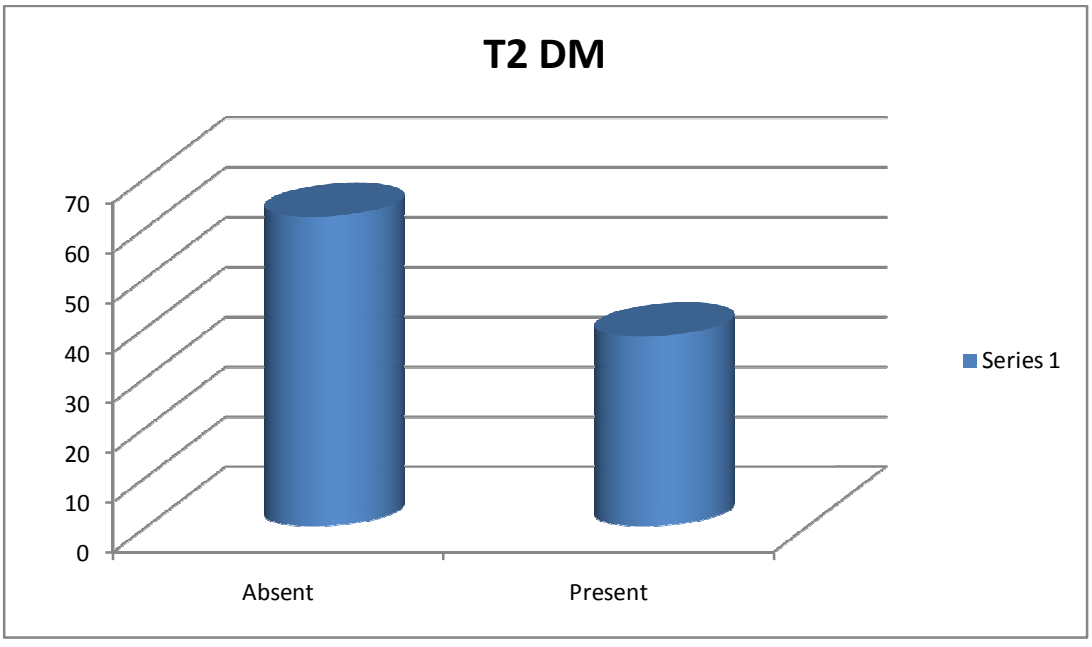
Fasting Plasma Glucose : 126 mg/dl.

2 Hours post prandial plasma glucose :200 mg/dl.

HbA1C :>6.5%.

Among the 50 CKD patients studied 19 patients were found to be present with T2 Diabetes mellitus.

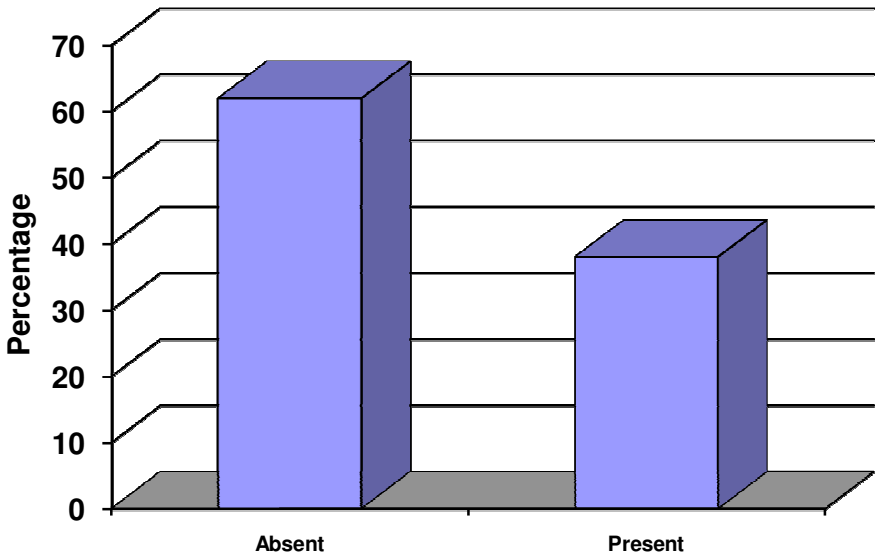
Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Absent	31	62.0
Present	19	38.0



Dyslipidemias

Among the 50 CKD patients Dyslipidemias were detected in 16 patients.

Particulars	No. of respondents (n=50)	Percentage (100%)
Absent	34	68.0
Present	16	32.0



USG Evidence for chronic kidney disease

Ultrasound features of following were taken as evidence for chronic kidney disease

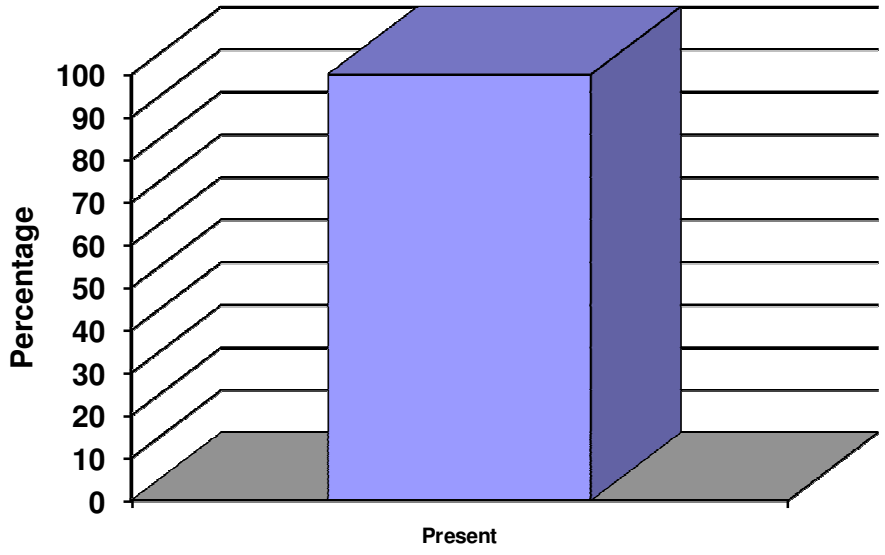
A] Bilateral contracted kidneys : Size less than 8cm in male patients and less than 7 cm in female.

B] Poor corticomedullary differtiantion.

C] Type II or III Renal parenchymal changes.

All 50 patients who have taken part in this study had ultrasound evidence For chronic kidney disease.

Particulars	No. of respondents (n=50)	Percentage (100%)
Present	50	100.0



ECG Evidence for presence of CAHD.

The following were taken as evidence for a CAHD.

1] ST elevation in men >40 years of age :At J point ≥2 mm in leads V2,V3;and >1mm in all other leads.In men <40 years of age threshold for ST elevation at J point is >2.5mm .

2]In women ,the threshold for abnormal ST elevation at J point is >1.5 mm in leads V2,V3 and >1mm in all other leads.

3]In right sided leads V3R,V4R threshold for abnormal ST elevation at J point is> 0.5mm,in males <30 years of age it is >1mm.

4]In posterior leads V7,V8,V9 the threshold for abnormal ST elevation at J point is 0.5mm.

A] Any Q wave in leads V2 and V3 >20 ms.

B] QS complex in leads V2 and V3.

C] Q wave >30 ms and >0.1 mv in V1-V2 and R: S >1 with a concordant positive T wave in the absence of a conduction defect.

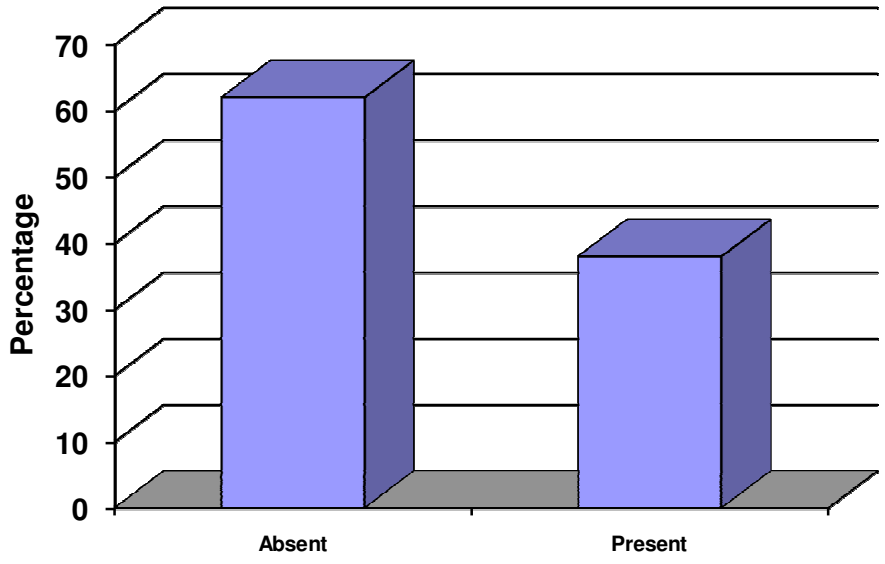
D] Presence of inverted T waves&associated convex ST segment.

E] R wave amplitude in lead V 3 is equal to or less than 3 mm.

F] Reversed R wave progression characterized by R in V4 < R in V3 or R in V3 < R in V2 or R in V2 < R in V1or a combination of these changes.

Among the 50 patients who were part of this study 18 patients were found to have evidence of coronary artery heart disease in ECG.

Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Absent	32	64.0
Present	18	36.0



ECHO Evidence for CAHD

The following features on ECHO by M – Mode and 2 – D Echo were taken as indicative of CAHD:

A] Abnormal systolic wall motion.

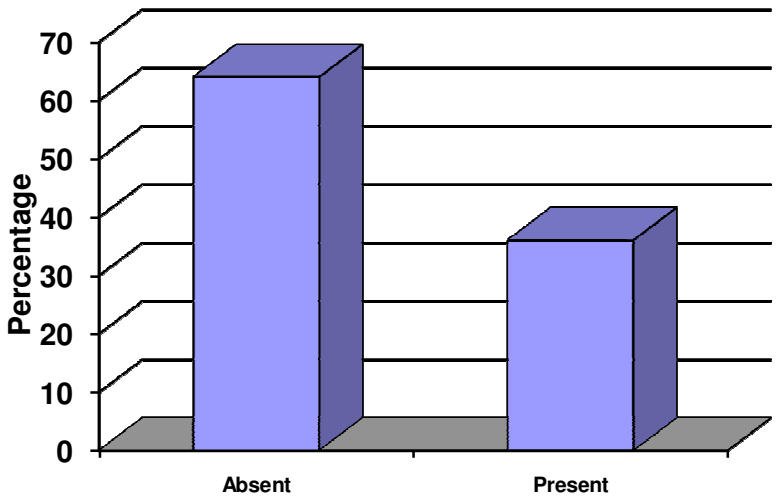
B] Systolic wall thickening.

C] Segmental wall motion abnormalities.

D] Ejection fraction < 55%.

Among the 50 patients who were part of this study 18 patients had echocardiographic evidence of coronary artery heart disease.

Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Absent	32	64.0
Present	18	36.0

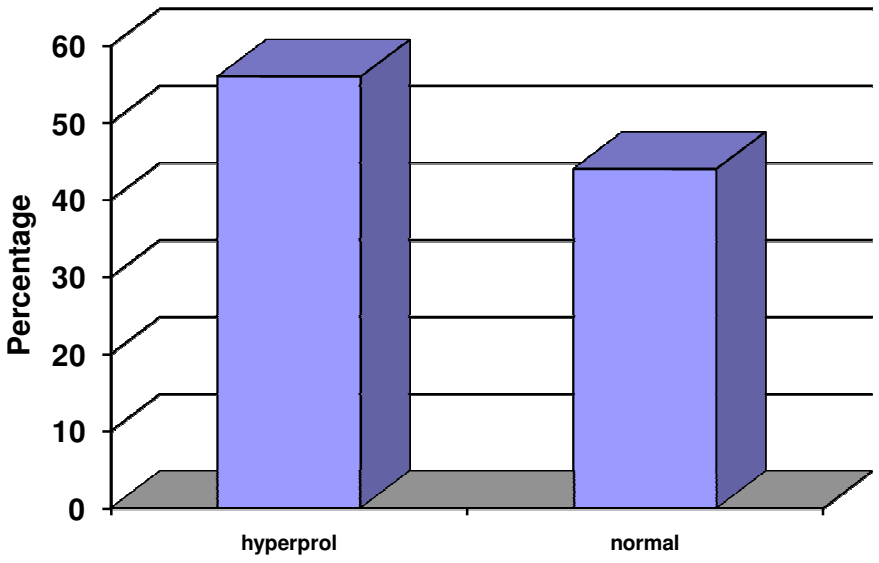


Serum Prolactin

Serum prolactin level was measured for the 50 patients with chronic kidney disease using fully Automated Bidirectionally Interfaced Chemi luminescent Immuno Assay [C.L.I.A].

Among the 50 CKD patients 28 patients had raised serum prolactin levels

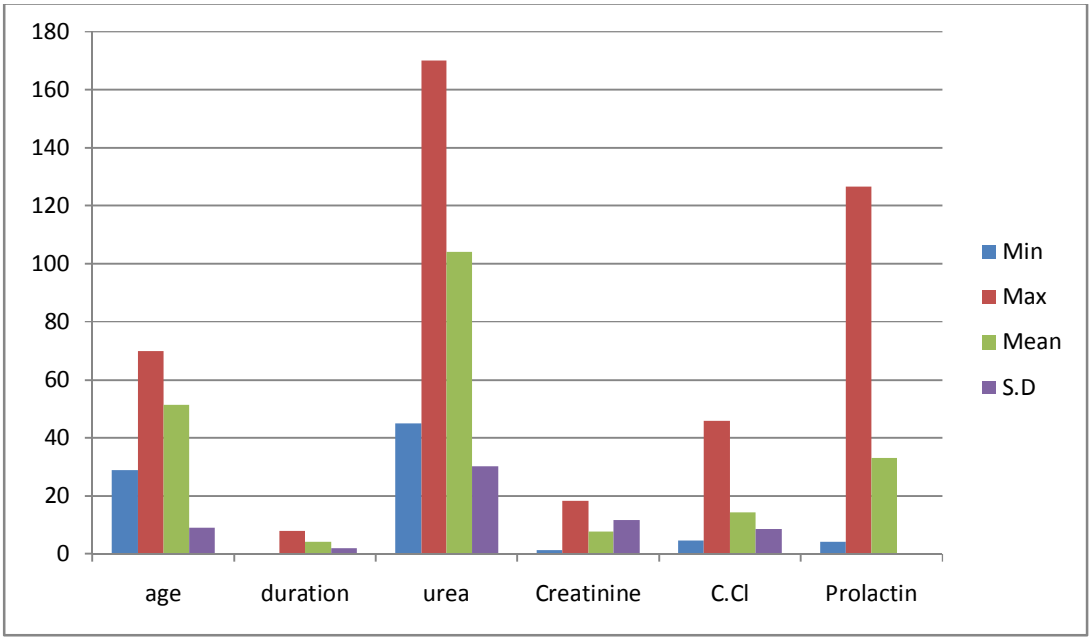
Particulars	**No. of respondents (n=50)**	**Percentage (100%)**
Positive	28	56.0
Negative	22	44.0



Descriptive statistics

Upon summarizing the study of 50 CKD patients following data could be obtained.

Item	Min.	Max.	Mean	S.D
Age	29	70	51.46	9.197
Symptom Duration	½	8	4.44	2.052
Urea	45.00	170.00	104.1200	30.30366
Creatinine	1.50	18.4	7.9500	11.79824
Creatinine Clearance ml /mm	4.77	46.00	14.5244	8.68455
Serum Prolactin (ng / ml)	4.27	126.59	33.2369	30.67783



Significance of association between serum prolactin levels and age distribution of patients with CKD

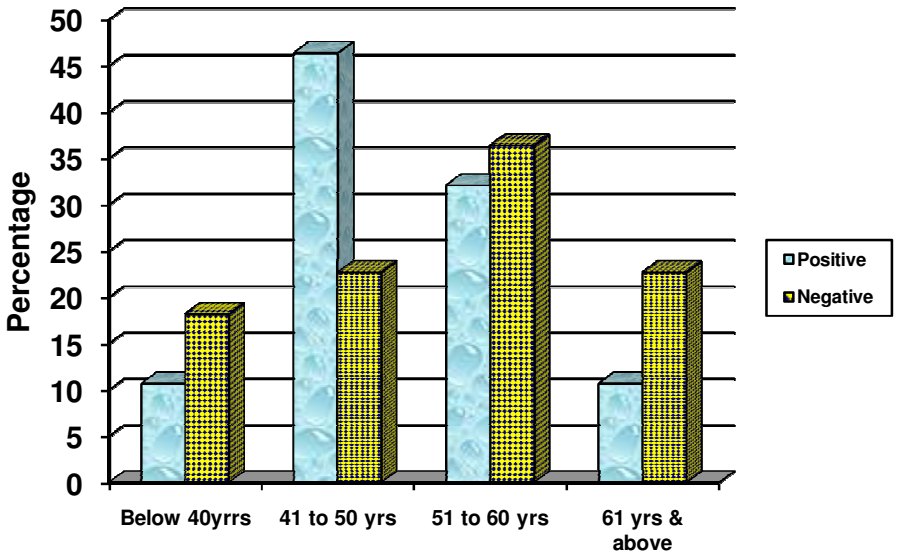
Chi – Square test, Serum Prolactin [ng/ml]

Age	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Below 40yrs	3	10.7%	4	18.2%	7	14.0%	X^2=3.589 Df=3 .309>0.05 Not Significant
41 to 50yrs	13	46.4%	5	22.7%	18	36.0%	
51 to 60yrs	9	32.1%	8	36.4%	17	34.0%	
61yrs & above	3	10.7%	5	22.7%	8	16.0%	

From statistical analysis serum prolactin levels did not show any significant association with age of the CKD patients.

CHI – SQUARE TEST

SERUM PROLACTIN (ng / ml) - AGE



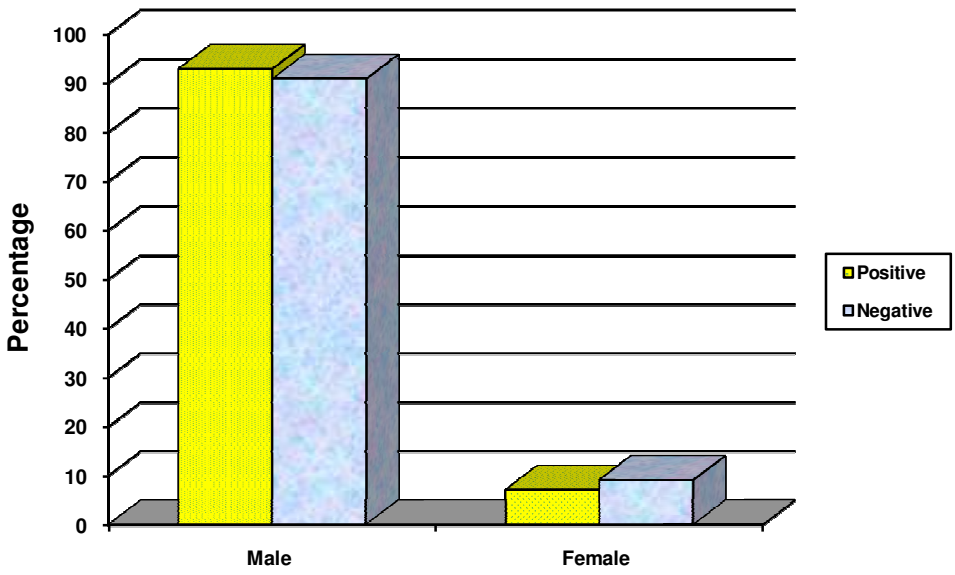
Significance of association between sex of the CKD patients and serum prolactin levels

Chi – square test, Serum Prolactin [ng/ml]

Sex	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Male	26	92.9%	20	90.9%	46	92.0%	X^2=.064 Df=1 .801>0.05
Female	2	7.1%	2	9.1%	4	8.0%	Not Significant

From the statistical analysis of above data there is no significant association between serum prolactin levels and sex of the CKD patients.

CHI – SQUARE TEST, SERUM PROLACTIN (ng / ml) - SEX



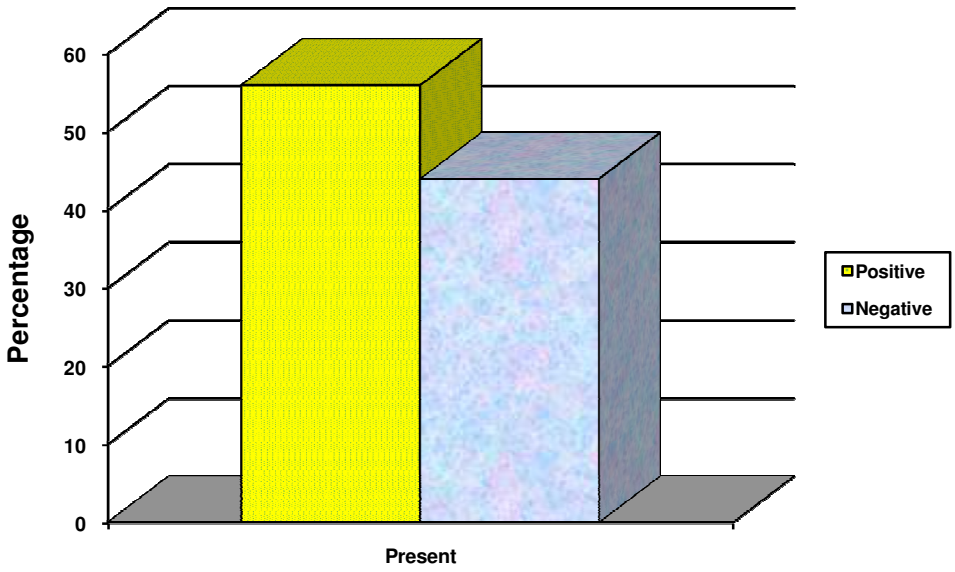
Significance of association between CKD patients with systemic hypertension and increased serum prolactin levels

Chi – Square Test, Serum Prolactin levels [ng/ml]

SHT	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Present	28	56%	22	100.0%	50	44.0%	-

No statistically significant association could be found between the CKD patients with systemic hypertension and increased serum prolactin levels.

CHI – SQUARE TEST
SERUM PROLACTIN (ng / ml) - SHT



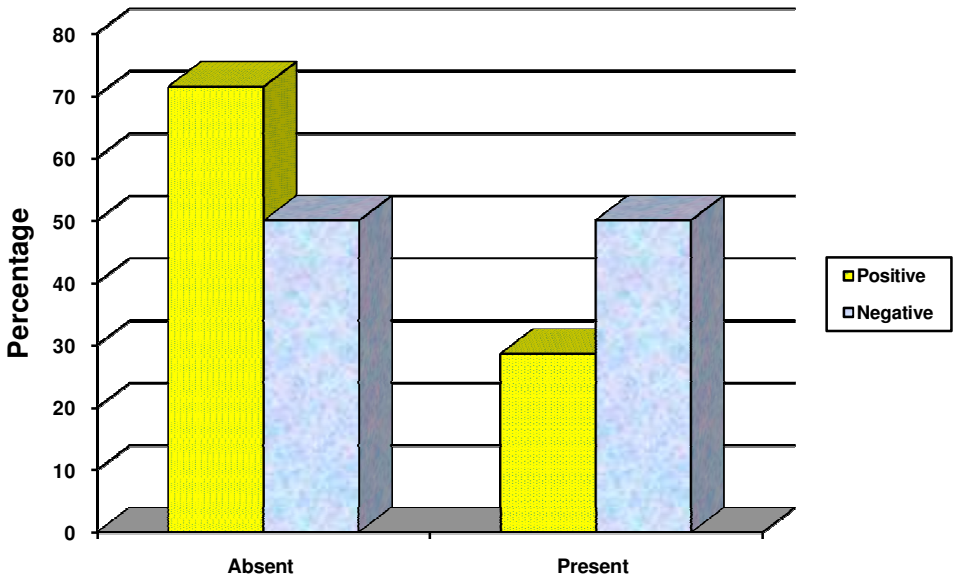
Significance of association between Diabetic patients with chronic kidney disease and increased serum prolactin levels

Chi – Square Test, Serum Prolactin levels [ng/ml]

T2 DM	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Absent	20	71.4%	11	50.0%	31	62.0%	X^2=2.401 Df=1 .121>0.05 Not Significant
Present	8	28.6%	11	50.0%	19	38.0%	

No statistically significant association could be established between the chronic kidney disease patients with T2 diabetes mellitus and increased serum prolactin levels.

CHI – SQUARE TEST, SERUM PROLACTIN (ng / ml) - T2DM



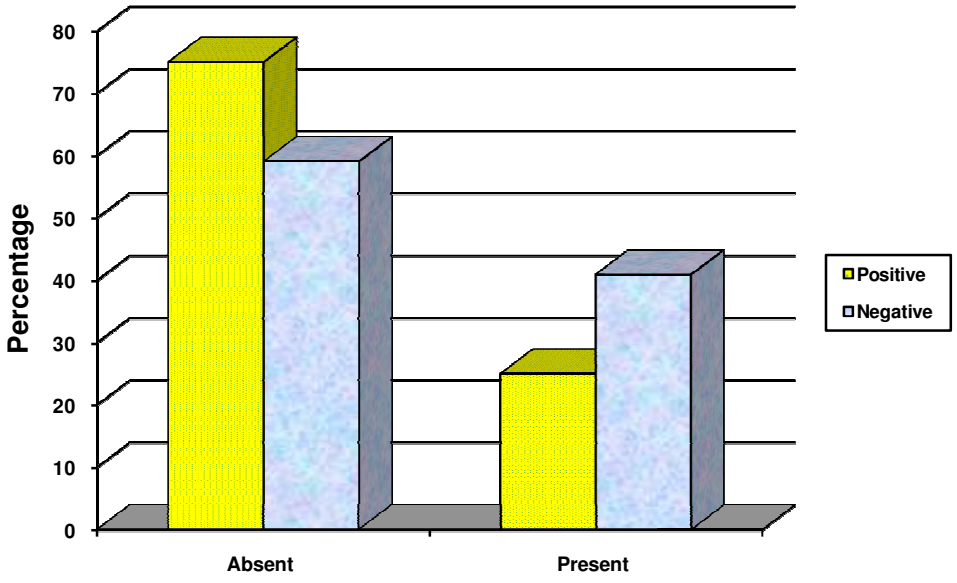
Significance of association between Dyslipidemia in CKD patients and increased serum Prolactin levels

Chi – square Test, Serum Prolactin [ng/ml]

DLM	Hyperprolctinemia Positive		Hyperprolactinemia Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Absent	21	75.0%	13	59.1%	34	68.0%	X^2=1.433 Df=1 .231>0.05 Not Significant
Present	7	25.0%	9	40.9%	16	32.0%	

No statistically significant association could be drawn between dyslipidemia in CKD patients and increased serum prolactin levels.

CHI – SQUARE TEST, SERUM PROLACTIN (ng / ml) – DLM



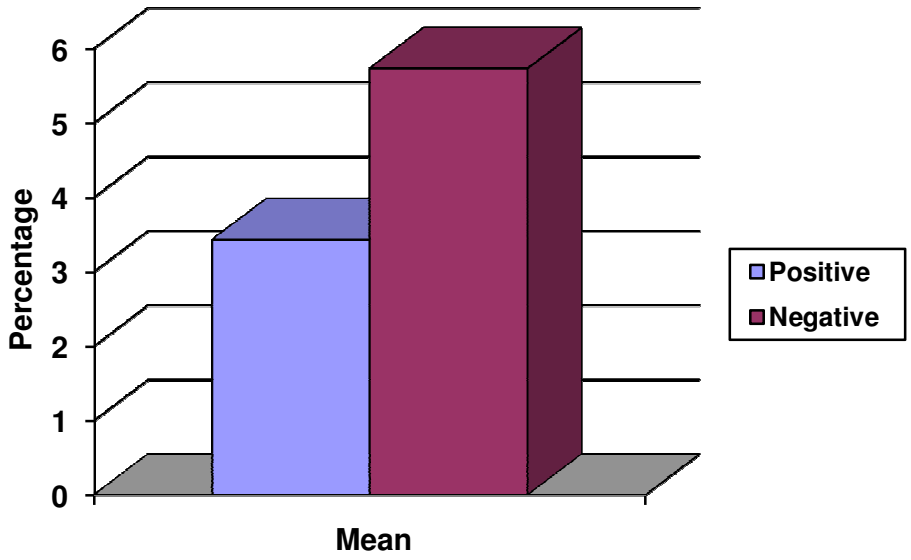
Significance of association between Chronic Kidney Disease and increased serum Prolactin levels

T – Test, Serum Prolactin levels [ng/ml]

Hyperprolactinemia	**Mean**	**S.D**	**Statistical inference**
Positive (n=28)	3.43	1.620	T=-4.704 Df=48 .000<0.05 **Significant**
Negative (n=22)	5.73	1.830	

According to Statistical analysis of data using T – Test there is a significant association between increased serum prolactin levels and presence of Chronic Kidney Disease.

T- TEST, SERUM PROLACTIN – Chronic Kidney Disease



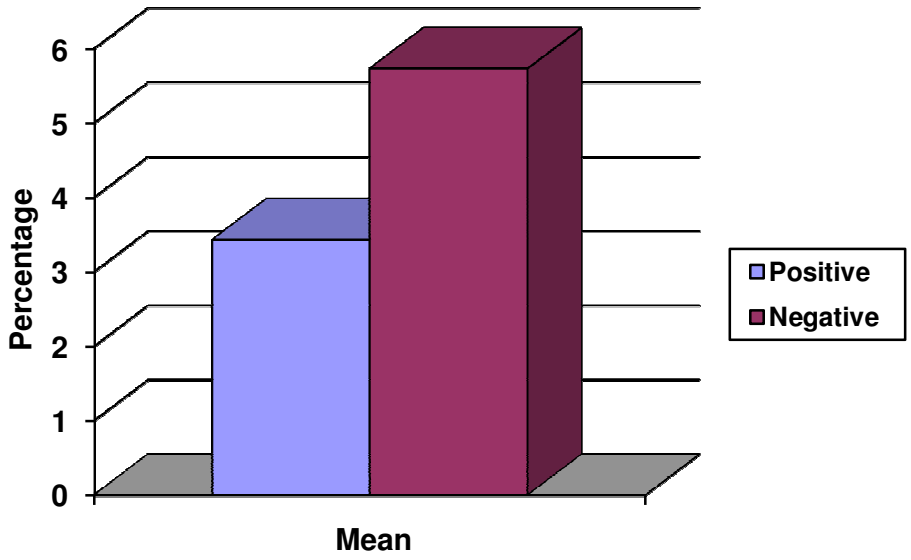
Significance of association between blood urea levels in Chronic Kidney Disease Patients and increased serum prolactin levels

T-Test, Serum Prolactin levels [ng/ml]

Urea	**Mean**	**S.D**	**Statistical inference**
Positive (n=28)	111.1071	31.86934	T=1.887 Df=48 .065>0.05 Not Significant
Negative (n=22)	95.2273	26.24778	

As per the T – Test no significant association could be established between raised blood urea levels in patients with chronic kidney disease and increased serum prolactin levels.

T- TEST, SERUM PROLACTIN – Urea



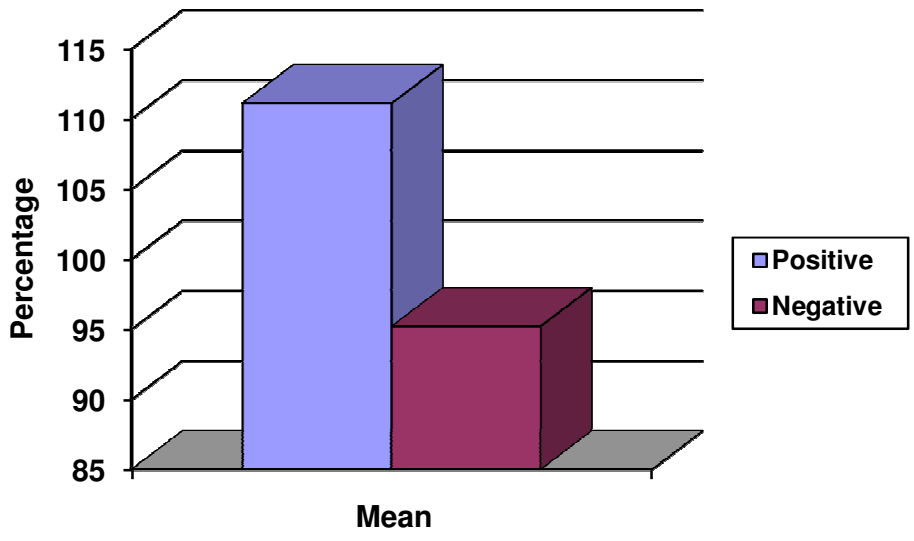
Significance of association between serum creatinine levels and increased serum prolactin levels

T –Test, Serum Prolactin levels [ng/ml]

Creatinine	Mean	S.D	Statistical inference
Positive (n=28)	7.4250	4.48757	T=-.352 Df=48 .727>0.05 Not Significant
Negative (n=22)	8.6182	17.26468	

According to the results of T test no significant association could be established between serum creatinine levels in patients with chronic kidney disease and increased serum prolactin levels among them.

T- TEST, SERUM PROLACTIN – Creatinine



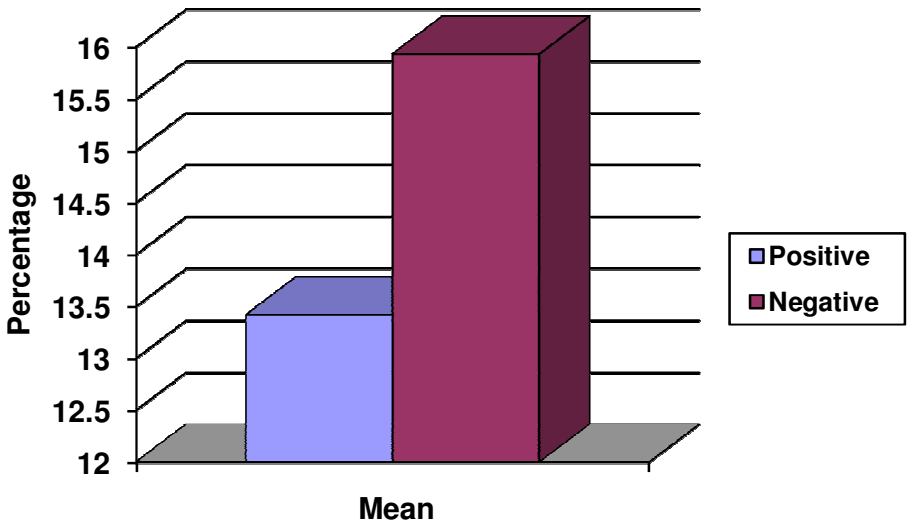
Significance of association between creatinine clearance and increased serum prolactin levels in patients with chronic kidney disease

T – Test, Serum Prolactin [ng/ml]

Creatinine Clearence ml /min	Mean	S.D	Statistical inference
Positive (n=28)	13.4182	9.28529	T=-1.016 Df=48 .315>0.05 Not Significant
Negative (n=22)	15.9323	7.83744	

As per the statistical analysis using T – Test there was no significant association between creatinine clearance in CKD patients and increased serum prolactin values in them.

T- TEST, SERUM PROLACTIN – Creatinine Clearence



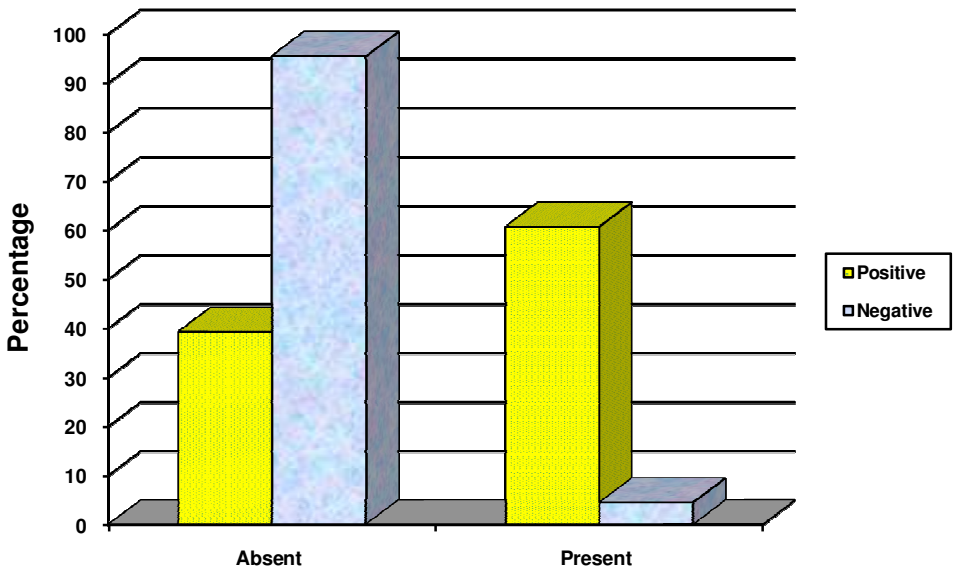
Significance of association between serum prolactin levels and coronary artery heart disease using ECG

ECG evidence for CAHDChi-square test, Serum Prolactin (ng / ml)

ECG	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Absent	11	39.3%	21	95.5%	32	64.0%	X^2=16.870 Df=1 .000<0.05 Significant
Present	17	60.7%	1	4.5%	18	36.0%	

According to the statistical analysis there was a significant association between increased serum prolactin levels and ECG evidence of CAHD.

CHI – SQUARE TEST, SERUM PROLACTIN (ng / ml) – ECG evidence for CAHD

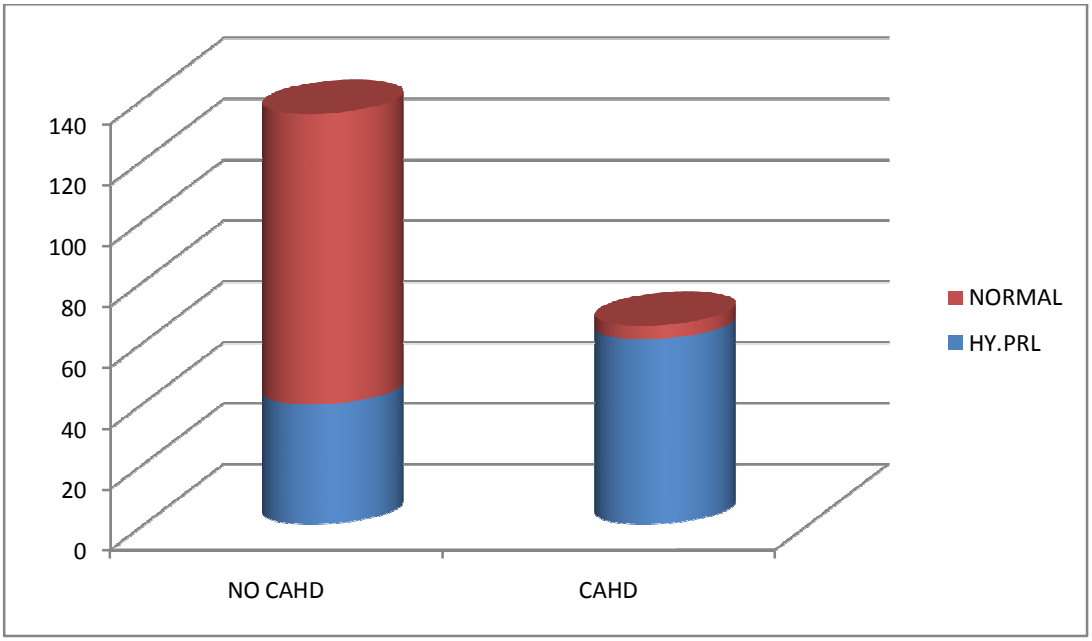


ECHO evidence for CAHD

Chi-square test, Serum Prolactin (ng / ml)

Echo	Positive		Negative		Total		Statistical inference
	(n=28)	*(100%)*	*(n=22)*	*(100%)*	*(n=50)*	*(100%)*	
Absent	11	39.3%	21	95.5%	32	64.0%	X^2=16.870 Df=1 .000<0.05 Significant
Present	17	60.7%	1	4.5%	18	36.0%	

According to the statistical analysis there was a significant association between increased serum levels of prolactin and ECHO evidence of CAHD.



DISCUSSION

Hyperprolactinemia in CKD patients

The kidneys are an important component in regulating endocrine systems in the body. The kidneys themselves produce certain hormones .Hormones like erythropoietin and calcitriol are examples for the above[77]. Kidneys also play an important role in the metabolism of some hormones .Kidneys also play an important role in the degradation of certain hormones. Hormones like insulin and cortisol are examples for the above.

In chronic kidney disease patients following abnormalities are noted pertaining to various endocrine systems in the body. There are alterations in signal feedback mechanisms of various hormones in the body. In addition alteration of hormonal production also occurs. In addition changes also occur in transport, protein binding and metabolism of hormones. In addition elimination of various hormones also gets altered in patients with chronic kidney disease.

In addition patients with chronic kidney disease also suffer from various other conditions. These include Protein energy malnutrition, a state of chronic inflammation, multiple drug intake, and presence of metabolic acidosis. Most importantly there is disturbance in the hypothalamic – pituitary – gonadal axis in patients with chronic kidney disease[78].

One of the major endocrine abnormalities detected in patients with chronic kidney disease is increased serum prolactin levels. Several studies have shown that serum prolactin levels remain elevated in patients with chronic kidney disease .This increase occurs in both male and female patients with chronic kidney disease. It has a prevalence of about 30 % to 65%[3,8].This is thought to be mainly due to reduced clearance by the kidneys[8]. There is alteration in the dopaminergic activity in patients with chronic kidney disease. Three is increased production of prolactin hormone[9,10]. This also contributes to the increased prolactin levels seen in this group of patients.

In our study we studied 50 patients with chronic kidney disease .In our study all patients were on conservative management. Many studies have been conducted for correlation between serum prolactin levels in CKD patients.

A Similar study of evaluating serum prolactin levels in chronic renal failure patients, CRF patients on haemodialysis and transplant recipients was conducted by R Peces & S Casado et all[72]. In this study R Peces & S Casasdo et all[72] conducted serum prolactin estimation in twelve patients of chronic kidney disease who were on conservative line of treatment and thirty patients of chronic kidney disease who were on

haemodialysis and nineteen patients of chronic kidney disease who were post transplant recipients with a functioning kidney.

At the end of their study authors have shown that basal levels of serum prolactin remain elevated in patients with chronic kidney disease .This increased serum levels of hormone prolactin was demonstrated in both CKD patients who were on conservative line of treatment and in CKD patients who were on haemodialysis.In their study the authors also demonstrated that the elevated serum prolactin hormone level showed a blunted and delayed response to stimulation with TRH.In this study R Peces & S Casado et all also have shown that Serum prolactin levels remain normal in those CKD patients who have received a transplant with functioning kidney. In this study authors have attributed the increased serum prolactin hormone levels to decreased renal catabolism and impaired hypothalamo – pituitary regulation.

As with other studies in our study also serum prolactin level was found to be elevated in 56 % of CKD patients. Remaining 44 % had normal serum prolactin levels.

A similar study of evaluating hyperprolactinemia and impaired pituitary response to suppression and stimulation in patients with chronic kidney disease was conducted by V.S.Lim , S.C.Kathpalia and L. Frohaman[1] .In this study authors also analyzed the reversibility of the

above mentioned abnormalities with Renal transplantation. In this study authors have demonstrated increased basal serum prolactin levels in patients with chronic kidney disease .In this study authors also have demonstrated that Prolactin hormone showed lack of responsiveness to suppressive as well as stimulatory agents .They attributed this lack of responsiveness to pathology at the pituitary either at the level of receptor binding or a post receptor level.

A similar study of Abnormalities in the regulation of serum prolactin hormone levels in patients with chronic kidney disease was conducted by German Ramirez, William M. O Neill, JR.H.Allan Bloomer and William Jubiz[77].In this study authors have studied the serum levels of prolactin hormone in patients with chronic kidney disease who were treated with haemodialysis.They also studied the regulation of prolactin hormone secretion in patients with chronic kidney disease.At the end of their study authors have concluded that basal serum levels of prolactin hormone remained elevated in patients with chronic kidney disease .Authors also demonstrated that this increased serum prolactin levels failed to suppress significantly following the administration of L – Dopa.This increased serum prolactin hormone levels also failed to show an increase in response to chlorpromazine and also to thryotropin releasing hormone.They concluded that serum prolactin hormone levels

increase in patients with chronic kidney disease and it is also abnormally regulated in these population.

Our study is consistent with results of above mentioned studies in that in our study basal serum levels of hormone prolactin remained elevated in 56 % of CKD patients. There was a statistically significant association between increased serum prolactin levels and presence of chronic kidney disease.

Hyperprolactinemia and the risk of Coronary Artery Heart Disease

From several studies conducted recently it has been shown that increased serum prolactin levels are commonly found abnormality in patients with Chronic Kidney Disease. However there are only limited numbers of studies available regarding the implications of this increased serum prolactin levels in patients with chronic kidney disease. The only few studies conducted in last decade on the consequences of this increased serum prolactin levels in patients with chronic kidney disease were mainly focused on the reproductive and sexual dysfunction .

Evidences from several studies conducted in non – renal population are accumulating which shows Prolactin may have several other actions other than what has already been well described. From these

studies it has been shown that Prolactin is having actions on several other biological systems as well which accelerate the process of atherosclerosis.

Increased serum levels of hormone prolactin have been observed in patients with essential hypertension[7,79].

The role of prolactin in essential hypertension was studied by J R Sowers, M Nyby et all[79] in their study, Dopaminergic control of prolactin and blood pressure: Altered control in essential hypertension. In their study authors examined the influence of dopamine on plasma catecholamine levels and plasma prolactin levels .The authors studied the mean arterial pressure response to upright posture .They also studied the mean arterial pressure response to isometric hand grip exercise. They analyzed the recumbent circadian prolactin and mean arterial pressure patterns in essential hypertension. In their study authors observed that a prolactin response to posture and isometric exercise in patients with essential hypertension. This was not observed in normotensive individuals. In this study authors also observed mean prolactin levels in patients with essential hypertension to be significantly higher over a 24 - hour recumbent period. In their study authors also observed that Treatment with bromocriptine had a lowering effect on mean arterial pressure levels throughout the 24 hours in the hypertensive group.Bromocriptine also eliminated the circadian rhythm of Prolactin

secretion. Thus at the end of their study authors conclude that circadian variations in prolactin secretion and blood pressure appear to be modulated by a central and / or peripheral dopaminergic mechanism .Decreased dopaminergic activity in essential hypertension may account, in part, for aberrances in prolactin secretion and systemic hypertension.

In addition it has been shown that prolactin plays a role in systemic hypertension in post menopausal women. It has also been shown that prolactin plays a role in arterial stiffness in post menopausal women.

This was studied by George A .Georgiopoulos, Kimon S. Stamatelopoulos , Irene Lambrinoudaki et all[80] ;They studied the relationship between increased serum prolactin levels and preclinical atherosclerosis in menopausal women with cardiovascular risk factors.In this study authors have demonstrated significant correlation between increased serum prolactin levels and arterial blood pressure.In this study significant association was found between increased serum prolactin levels and central aortic systolic blood pressure.Significant correlation was also demonstrated between increased serum prolactin levels and central aortic diastolic blood pressure. Increased serum prolactin levels also had significant correlation with aortic pulse wave velocity. Aortic pulse wave velocity is a marker for aortic stiffness. By statistical analysis increased serum prolactin levels predicted the long term risk of systemic

hypertension .It also predicted the long term risk of aortic stiffness. At the end of this study authors have arrived at a conclusion that increased serum prolactin levels play a role in accelerating the process of arteriosclerosis in females with early menopause. Possible mechanism behind this may be by prolactin affecting central and peripheral blood pressure and by facilitating the arterial stiffness.

From several studies it has been shown that serum prolactin levels increase in patients during the acute phase of coronary syndromes[11]. In addition increased serum prolactin levels have also been demonstrated in patients with ischemic stroke[12,13].

In a study by Robin Haring ,Nele Friedrich et all[81] positive association of serum prolactin concentrations with all – cause and cardiovascular mortality was studied by authors. In their study authors reported an independent positive association of serum prolactin concentrations with all – cause mortality. Authors also established an independent positive association between serum prolactin concentration and cardiovascular mortality.

Raised serum prolactin has been shown to play a causative role in hypertensive complications of patients with preeclampsia[14,15]. In addition it has been shown that increased serum prolactin plays a causative role in

the development of heart failure that accompanies peri and post partum cardiomyopathy[16].

In another study increased serum prolactin levels predicted adverse cardio vascular events in male patients with erectile dysfunction[17].

In another study by Anne Q Reuwer , Marco Van Eijk ,et all[18] the authors demonstrated prolactin receptors in the atherosclerotic plaques which they obtained from human carotid arteries. In this study through in situ hybridization techniques authors demonstrated the presence of prolactin receptors in mononuclear cells of atherosclerotic plaques. Using immunohistochemical analysis and immunoelectron microscopy authors demonstrated the abundant presence of prolactin receptors in the macrophages near the lipid core of the atherosclerotic plaques .Prolactin receptors were also abundantly detected in the macrophages near the shoulder region of the atherosclerotic plaques. At the end of their study authors conclude that Prolactin receptors are increasingly expressed in macrophages of the atherosclerotic plaques at sites of most prominent inflammation. Finally authors conclude that prolactin receptor signaling contributes to the local inflammatory response within the atherosclerotic plaque .This aggravates the process of atherogenesis.

In another study by Dilek Yavuz, Oguzhan Deyneli, Ishan Akpinar et all [6]Endothelial function, insulin sensitivity and inflammatory markers in hyperprolactinemic pre – menopausal women were studied in detail[6]. In this 16 hyperprolactinemic patients were taken for study. They studied insulin sensitivity among the study group. Endothelial function was studied using flow mediated dilatation technique. The authors finally concluded that hyperprolactinemic state was associated with impaired endothelial function .It was also shown to be associated with decreased insulin sensitivity. Both the above factors contribute to process of atherosclerosis. The increased serum prolactin levels may contribute to the early atherosclerosis in this patient group. Correction of this increased serum prolactin level was associated with improvement in endothelial function .It also improves insulin sensitivity among them.

Hyperprolactinemia in CKD patients and the risk of coronary artery heart disease

Prolactin levels, endothelial dysfunction and the risk of cardiovascular events and mortality in patients with CKD were extensively studied by Juan jesus carrero, John Kyriazis ,Alper Sonmez et all[4].

We conducted an observational study .In our study we evaluated serum prolactin levels in 50 patients with chronic kidney disease and we

further evaluated the association between increased serum prolactin levels and the risk of coronary artery heart disease.

In the study by Juan Jesus Carrero et all[4] the authors conducted an observational study in two cohorts.One cohort of 457 nondialyzed CKD patients and another cohort of 173 CKD patients who were on haemodialysis.In their study authors measured the serum levels of hormone prolactin in both cohorts. To assess the cardiovascular risk in non – dialyzed CKD patients' authors conducted assessments with Flow mediated dilatation [FMD] and Carotid intima – media thickness [IMT], In Chronic Kidney Disease patients who were on haemodialysis authors did the assessment with Pulse Wave Velocity [PWV].

In their study Authors demonstrated an increase in serum prolactin levels in both non – dialyzed CKD patients and in CKD patients who were on haemodialysis.In their study, in non – dialyzed CKD patients, every 10 ng/ml increase in serum prolactin raised the risk of suffering an adverse cardiovascular

Event by 27 %.It had a hazard ratio of 1.27.In their study authors have shown in second cohort of CKD patients who were on haemodialysis ,every 10 ng/ml increase in serum prolactin level increased the risk of mortality due to cardiovascular disease by 15 %.It had a hazard ratio of 1.15.In their study authors also described an association between

hyperprolactinemia and endothelial dysfunction as measured by flow – mediated dilatation [FMD].They also described an association between hyperprolactinemia and arterial stiffness as assessed by Pulse wave velocity.

In our study we did an estimation of serum prolactin level in 50 chronic kidney disease patient's .Among the 50 CKD patients 28 had elevated serum prolactin levels which was about 56%.Increased serum prolactin levels had an statistically significant association with presence of chronic kidney disease.

We further did an analysis about presence of coronary artery heart disease in patients with increased serum prolactin levels .We did that by doing ECG and ECHO analysis of patients who show an increased serum prolactin level.

In our study among the 28 CKD patients with hyperprolactinemia 17 patients had coronary Artery Heart Disease as diagnosed by using ECG & ECHO which is about 60.7%.This also showed a statistically significant association to exist between hyperprolactinemic CKD patients and occurrence of CAHD among them.

LIMITATIONS OF OUR STUDY

- Our study was observational in nature.
- In our study we could not determine Prolactin is a risk factor per se or whether it is an intermediate in larger pathological pathway.
- Increased serum prolactin level in patients with chronic kidney disease leads to decreased gonadotropin levels with consequent testosterone deficiency. This reduction in testosterone may also be a contributory factor for accelerated atherosclerosis and increased risk of CAHD.
- Increased serum levels of hormone prolactin may also be a consequence of reduced dopaminergic activity. This would have resulted in increased noradrenaline release .This would have resulted in endothelial dysfunction and adverse cardiovascular outcome.

CONCLUSION

50 patients of chronic kidney disease who were on conservative line of treatment were taken for study. Serum prolactin levels were measured in them .They were evaluated for presence of Coronary Artery Heart Disease using ECG and ECHO. The association between hyperprolactinemia in CKD patients and occurrence of Coronary Artery Heart Disease among them was studied.

The following conclusions were arrived from our study

- Chronic Kidney Disease is associated with increased serum levels of hormone prolactin [Hyperprolactinemia].
- Hyperprolactinemia could be detected in 56 % of our study group of patients with chronic kidney disease.
- Among the CKD patients with hyperprolactinemia about 60.7% had evidence of Coronary Artery Heart Disease when evaluated using ECG and ECHO.
- From our study we could conclude that hyperprolactinemia in patients with chronic kidney disease may be a risk factor for future risk of Coronary Artery Heart Disease.
- Further studies are needed to confirm this finding.

BIBLIOGRAPHY

1. Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure:reversal after transplantation. Lim Vs,Kathpalia SC,Frohman LA .Journal of clinical Endocrinology & metabolism ,1979;48:101-107 [pubmed].

2. Non puerperal galactorrhoea and hyperprolactinemia. Gomez F;Reyes FI,Faiman C .American journal of medicine 1977;62:648-660 [pubmed].

3. Hyperprolactinemia in patients with renal insufficiency and chronic renal failure requiring haemodialysis or chronin ambulatory peritoneal dialysis. Hou SH,Grossman S,Molitch ME .American journal of kidney diseases 1985;6:245-249 [pubmed].

4. Prolactin levels , endothelial dysfunction , and the risk of cardiovascular events and mortality in patients with CKD , Carrero JJ, Kyriazis J, Sonmez A,Tzanakis I, Quereshi AR,Stenvinkel P,et all, Clinical journal of American society of Nephrology ,2012;207-15.

5. Sexual dysfunction in Uremia,Biff F.Palmer,Journal of American society of Nephrology,1999,10:1381-1388.

6. Endothelial function ,insulin sensitivity and inflammatory markers in hyperprolactinemic pre – menopausal women,Dilek Yavuz, Oguzhan Deyneli, Ishan Akpinar, Erdem Yildiz, Hulya Gozu,Ozlem Sezgin, Goncagul Haklar and SemaAkalin.European journal of Endocrinology.2003.

7. Hyperprolactinemia and antihypertensive effect of bromocriptine in essential hypertension.Identification of abnormal central dopamine control . Stumpe KO,Kolloch R,Higuchi M,Kruck F,Vetter H : Lancet 2: 211-214,1977.

8. Macroprolactinemia does not contribute to elevated levels of prolactin in patients on renal replacement therapy. Yavuz D,Topcu G,Ozener C,Akalin S,Sirikoi O:Clinical Endocrinology [Oxford] 63 : 520-524,2005 [pubmed].

9. Prolactin metabolic clearance and resistance to dopaminergic suppression in acute uremia. Mckenna TM,Woolf PD : Endocrinology 116 :2003-2007,1985[pubmed].

10. Total body zinc depletion and its relationship to the development of hyperprolactinemia in chronic renal insufficiency, Caticha O, Norato DY, Tambascia MA, Santana A, Stephanou A, Sarlis NJ :Journal of Endocrinological investigation 19 :441-448,1996[pubmed].

11. Increased prolactin in acute coronary syndromes as putative co – activator of ADP – stimulated P – selectin expression . Raaz D,Wallaschofski H,Stumpf C , Yilmaz A,Cicha I,Klinghammer L,Daniel WG,Lohmann T,Garlichs CD : Hormone and Metabolic research 38 : 767-772,2006[pubmed].

12. Enhanced platlet activation by prolactin in patients with ischemic stroke. Wallaschofski H,Lohmann T,Hild E,Kobsar A,Siegemund A,Spilcke – Liss E,Hentschel B,Stumpf C,Daniel WG,Garlichs CD,Eigenthaler M : Thrombosis and Haemostasis 96 :38-44,2006.

13. Hyperprolactinemia in patients on antipsychotic drugs causes ADP – Stimulated platlet activation that might explain the increased risk for venous thromboembolism : Pilot study . Wallaschofski H, Eigenthaler M, Kiefer M, Donne M, Hentschel B,Gertz HJ,Lohmann T : Journal of clinical psychopharmacology 23 : 479-483,2003[pubmed].

14. Role of prolactin in pregnancy hypertension . Marlettini MG,Cassani A,Morselli Labate AM,Rusticali AG,Crippa S,Trabatti M,Miniero R,Plate L,Orlandi C : Annals of clinical and experimental hypertension 9 : 1099-1119,1987[pubmed].

15. Urinary prolactin as a reliable marker for preeclampsia , its severity , and the occurrence of adverse pregnancy outcomes . Leanos – Miranda A,Marquez – Acosta J,Cardenas – Mondragon GM,Chinnolla – Arellano ZL,Rivera – Leanos R,Bermejo – Huerta s, Romero – Arauz JF,Alvarez - Jimenez G, Ramos – Leon JC,Ulloa – Aguirre A: Journal of Clinical Endocrinology and metabolism 93: 2492-2499,2008[pubmed].

16. A cathepsin D – cleaved 16 kDa form of prolactin mediates post partum cardiomyopathy. Hilfiker – Kleiner D, Kaminski K,Podewski E,Bonda T,Schaefer A,Sliwa K,Forester O,Quint A,Landmesser U,Doerries C,Luchtefeld M,Poli V,Schneider MD,Balligand JL,Desjardins F,Ansari A,Struman I,Nguyen NQ,Zschemisch NH,Klein G,Heusch G,Schulz R,Hilfiker A,Drexler H.:Cell 128:589-600,2007[pubmed].

17. Prolactin levels independently predict major cardiovascular events in patients with erectile dysfunction. Corona G, Rastrelli G,Boddi V,Monami M, Melani C, Balzi D, Sforza A, Forti G, Mannuci E,Maggi M.:International journal of Andrology 34 :217-224,2011[pubmed].

18. The Prolactin receptor is expressed in macrophages within human carotid atherosclerotic plaques : A role for prolactin in atherogenesis?,Anne Q Reuwer,Marco Van Eijk,Felicia M,Chris M Van der Loos,Nike Claessen, Peter Teeling,John J PKastelin, Jorg Hamann,Vincent Goffin,Jan H Von der Thusen,Marcel Th B Twickler and Jan Aten, Journal of Endocrinology,November 10 2010.

19. Prolactin levels and the risk of future coronary artery disease in apparently healthy men and women . Reuwer AQ,Twickler MT,Hutten BA,Molema FW,Wareham NJ,Dallinga – Thie GM,Bogorad RL,Goffin V,Smink - Bol M,Kastelein JJ,Boekholdt SM,Khaw KT : Circulation :Cardiovascular genetics 2 : 389-395,2009[pubmed].

20. Cardiovascular and non cardiovascular mortality among patients starting dialysis. De Jager DJ,Grootendorst DC,Jager KJ,Van Dijk PC,Tomas LM,Ansell D,Collart F,Finne P,Heaf JG,De

Meester J, Wetzels JF,Rosendaal FR,Dekker FW :Journal of American Medical Association 302 :1782-1789,2009[pubmed].

21. Chronic kidney disease and the risk of death , cardiovascular events and hospitalization. Go AS,Chertow GM,Fan D,Mc culloch CE, Hsu CY : New England Journal of Medicine 351 :1296-1305.2004.

22. Prolactin and growth hormone in patients with pituitary adenomas ,A correlative study of hormone in tumour and plasma by immunoperoxidase technique and radioimmunoassay. Zimmerman EA,Defendini R,Frantz AG,;Journal of clinical endocrinology and metabolism ,1974;38:577-585.

23. Effect of pregnancy on the somatotroph and the prolactin cell of human adenohypophysis. Goluboff LH,Ezrin C,Journal of clinical endocrinology and metabolism 1969 :29:1533-1541[pubmed].

24. Scheithauer BW,Sano T,Kovacs KT,Young WF Jr,Ryan N,Randall RV.The pituitary gland in pregnancy .A clinico pathologic and immunohistochemical study of 69 cases .Mayo clinic proceedings .1990;65:461-474.

25. Prager EM,Wilson AC,Lowenstein JM,Sarich VM.Genes for growth hormone , chorionic somatomammotropin ,and growth hormone like gene on chromosome 17 in humans.Science 1980;209:289-292.

26. Owerbach D,Rutter WJ,Cooke NE et all .The prolactin gene is located on chromosome 6 in humans.Science 1981;212:815-816.

27. Effects of estrogen on primary ovine pituitary cell cultures : Stimulation of prolactin secretion ,synthesis and preprolactin messenger ribonucleic acid activity.Vician L,Shupnik MA,Gorski J.Endocrinology 1979:104:736-743.

28. Estradiol regulates the transcription of prolactin gene.Maurer RA.Journal of biological chemistry.1982:257:2133-2136.

29. Thyroid hormone specifically inhibits prolactin synthesis and decreases prolactin messenger ribonucleic acid levels in cultured pituitary cells .Maurer RA.Endocrinology 1982:110:1507-1514.

30. Relationships between thyroid hormone and glucocorticoid effects in GH3 pituitary cells.Endocrinology 1980:106:600-605.

31. Transcriptional regulation of the prolactin gene by ergocryptine and cyclic AMP.Maurer RA.Nature 1981:294:1-3.

32. Adenosine 3'5' – monophosphate derivatives increase prolactin synthesis and prolactin messenger ribonucleic acid levels in ergocryptine treated pituitary cells.Maurer RA.Endocrinology : 1982:110:1957-1963.

33. Dopamine inhibits adenylate cyclase in human prolactin secreting adenomas.De camilli P,Macconi D,Spada A.Nature 1979:278:252-254.

34. Pharmacological characterization of the D2 dopamine receptor negatively coupled with adenylate cyclase in rat a.nterior pituitary.Enjalbert A,Bockeert J.Molecular pharmacology 1982:23:576-584.

35. Vasoactive intestinal peptide [VIP] stimulates prolactin [PRL]release and cAMP production in a rat pituitary cell line[GH3/B6]Additive effects of VIP and TRH on PRL release.Gourdji D,Bataille D,Vauclin N et all .FEBS letter 1979:104:165-168.

36. Regulation of prolactin secretion at the level of the lactotroph.Lamberts SWJ,MacLeod RM.Physiological reviews 1990:70:279-318.

37. Human prolactin cDNA structural analysis and evolutionary comparisons.Cooke NE,Coit D,Shine J,Baxter JD,Martial JA.Journal of biological chemistry 1981:256:4007-4016.

38. Glycosylated prolactin is a major circulating variant in human serum .Markoff E,Lee DW,.1987:65:1102-1106[pubmed].

39. The Proportion of glycosylated prolactin in serum is decreased in hyperprolactinemic states.Hashim IA,Aston R,Butler J.Journal of clinical endocrinology and metabolism 1990:71:111-115.

40. Glycosylation selectively alters the biological activity of prolactin.Endocrinology ,1988:123:1303-1306.

41. Factors influencing the secretion of human prolactin and growth hormone in menstrual and gestational women.Tyson JE,Freisen HG.American journal of obstetrics and gynaecology 1973 :116:377-387.

42. Human prolactin in plasma , amniotic fluid , and pituitary : identity and characterization by criteria of electrophoresis and isoelectric focusing in polyacrylamide gel .Ben – David M , Robert D,Bates RW,Bridson E,Chrambach A.Journal of clinical endocrinology and metabolism 1973:36:951-964.

43. Decidua : a Possible source of amniotic fluid prolactin.Riddich DH,Kumsik WF.American journal of obstetrics and gynaecology 1977:127:187-192.

44. A Radioimmunoassay for human prolactin.Proc Nat Acad Sci USA 1971:68:1902-1906.

45. A Homologous Radioimmunoassay for human Prolactin.Sinha YN,Selby FW,Lewis UJ,Vanderlaan WP,.Journal of clinical endocrinology and metabolism 1973:36:509-516.

46. A New sensitive and specific bioassay for lactogenic hormones : Measurement of prolactin and growth hormone in human serum .Tanaka T,Shiu RPC,Gout PW et all .Journal of clinical endocrinology and metabolism 1980:51:1058-1063.

47. Adenohypophysis has an inherent property for pulsatile prolactin secretion.Shin SH,Reifel CW.Neuroendocrinology 1981:32:139-144[pubmed].

48. Pulsatile release of growth hormone and prolactin from the primate pituitary in vitro.Stewart JK,Clifton DK,Koerker DJ,Rogol AD.Endocrinology 1985:116:1-5[pubmed].

49. Relation of sleep - entrained human prolactin release to REM – Non REM cycles.Parker DC,Rossman LG,Vanderlaan EF.Journal of clinical endocrinology and metabolism ,1973:38:646-651[pubmed].

50. The nocturnal rise of human prolactin is dependent upon sleep.Sassin JF,Frantz AG,Kapen S,Weitzman ED.Journal of clinical endocrinology and metabolism 1973:37:436-440[pubmed].

51. Acute prolactin release triggered by feeding.Quigley ME,Ropert JF.Journal of clinical endocrinology and metabolism 1981:52:1043-1045[pubmed].

52. Prolactin stimulation by protein is mediated by amino acids in humans.Carlson HE,Journal of clinical endocrinology and metabolism 1989 :69:7-14[pubmed].

53. Circulating levels of prolactin during the menstrual cycle.McNeilly AS,Chard T.Clinical endocrinology[oxf].1974:3:105-112[pubmed].

54. Prolactin levels during the menstrual cycle.Franchimont P,Dourcy C,Legros JJ.Clinical endocrinology[oxf].1976:5:643-650.[pubmed].

55. Pattern of increase in circulating prolactin levels during human gestation.Rigg LA,Lein A,Yen SSC.American journal of obstetrics and gynaecology 1977:129:454-456.[pubmed].

56. Factors influencing the secretion of human prolactin and growth hormone in menstrual and gestational women.Tyson JE,Freisen HG,American journal of obstetrics and gynaecology 1973:116:377-387.[pubmed].

57. Human prolactin and growth hormone release during surgery and other conditions of stress.Noel GL,Suh HK,Stone SJG,Frantz AE.Journal of clinical endocrinology and metabolism ,1972:35:840-851.

58. Effects of dopamine infusion on pituitary hormone secretion in humans.Leblanc H,Lachelin CL,Abu – Fadil S,Yen SSC.Journal of clinical endocrinology and metabolism .1976:43:668-674.

59. Functional studies of dopamine control of prolactin secretion in normal women and women with hyperprolactinemic pituitary microadenoma.Quigley ME,Judd SJ,Gilliland GB,Yen SC.Journal of clinical endocrinology and metabolism .1980:50:994-998.

60. Increased serum prolactin after administration of synthetic thyrotropin releasing hormone [TRH] in man.Jacobs LS,Snyder PJ,Wilber JF et all.Journal of clinical endocrinology and metabolism 1971:33:996-998.

61. Vasoactive intestinal peptide increases prolactin messenger ribonucleic acid content in GH3 cells.,Carrillo AJ,Pool TB,Sharp ZD,.Endocrinology 1985:116:202-206.

62. Effect of 5 – hydroxy tryptophan [5-HTP] on plasma prolactin levels in man.Kato Y,Nakai Y,Imura H et all. Journal of clinical endocrinology and metabolism 1974:38:695-697.[pubmed].

63. Prolactin releasing action of a low dose of exogenous gonadotropin – releasing hormone throughout the human menstrual cycle.Maris V,Melis GB,Paoletti AM,Strigini F.Neuroendocrinology 1986:44:326-330.[pubmed].

64. Histamine regulation of prolactin secretion through H1 and H2 receptors.Knigge U,Dejjard A,Wollesen F et all.Journal of clinical endocrinology and metabolism :1982:55:118-122.

65. Lactation in humans.Whitworth NS,Psychoneuroenocrinology 1988:13:171-188.

66. Hyperprolactinemia – a significant factor in female infertility.Kredentser JV,Hoskins CF,Scott JZ.American journal of obstetrics and gynaecology 1981:139:264-267.[pubmed].

67. Hyperprolactinemia and impotence.Franks S,Jacobs HS,Martin N,Nabarro JDN.Clinical endocrinology 1978:8:277-287.

68. Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure.Sievertsen GD,Lim VS,Nakawatse C,Frohman LA.Journal of clinical endocrinology and metabolism 1980:50:846-852.[pubmed].

69. Serum prolactin in liver disease and its relationship to gynaecomastia.Morgan MY,Jacobovits AW,Gore MB et all .Gut 1978:19:170-174.[pubmed].

70. Serum prolactin levels in untreated primary hypothyroidism.Honbo KS,Herle AJV,Kellett KA.American journal of medicine 1978:64:782-787.[pubmed].

71. Galactorrhoea and hyperprolactinemia associated with chest wall injury.Morley JE,Hodgkinson DH,Kalk WJ.Journal of clinical endocrinology and metabolism 1977:45:931-935.[pubmed].

72. Prolactin in Chronic Renal failure ,Haemodialysis, and Transplant recipients, R Peces,S Casado ,M Frutos , C Horcajada, J M Lopez – Novoa,L Hernando, Department of Nephrology , Fundacion Jimenez , Diaz , Madrid,Spain,Nephron journals,1981;28:11-16.Proc .Eur.Dial.Transplant .Assoc.1979:16:700-702.

73. Abnormalities in the regulation of Prolactin in patients with Chronic Renal Failure, German Ramirez, William M.O Neill,Jr.H.Allan bloomer and William jubiz,Journal of Clinical Endocrinology & Metabolism. Received: February 07, 1977,:45:658-661.

74. Improved sexual function in male haemodialysis patients on bromocriptine.Bommer J et all ,Lancet ii,496-498.[pubmed].

75. Chronobiological variations of prolactin [PRL] in Chronic Renal Failure[CRF].Biasioli,S.,MazzaliA,Foroni D'Andrea,G,Feriani,M.,Chiaramonte ,S,Cesaro A,and Micieli G.Clinical nephrology 30,86-92.

76. Hormonal profile in pubertal females with chronic renal failure before and under haemodialysis and after renal transplantation .Ferraris J,R.Domene,H.M.Escobar ,M,E.Caletti , M,Ramirez,J,A and Rivarola M.A.Acta endocrinologica 115,289-296.

77. Endocrine abnormalities associated with chronic renal faiure.Lim VS,Kathpalia SC,Henriquez C.Med Clin North Am .1978:62:1341-1346.[pubmed].

78. Gonadal dysfunction in men with chronic kidney disease.Clinical features , prognostic implications and therapeutic options.Iglesias P,Carrero JJ,Diez JJ. J.Nephrol 2012:25:31-42.[pubmed].

79. Dopaminergic control of prolactin and blood pressure : altered control in essential hypertension.J R Sowers,M Nyby ,and K Jasberg,Hypertension ;journal of American heart association:1982:4:431-437.

80. Prolactin and Preclinical atherosclerosis in Menopausal women with Cardiovascular Risk Factors.George A .Georgiopoulos, Kimon S .Stamatelopoulos, Irene Lambrinoudaki, Maria Lykka, Katerine Kyrkou, Dimitrios Rizos, Maria Creatsa, George Christodoulakos, Maria

Alvizaki, Petros P.Sfikakis,and Christopher Papamichael.Hypertension journal of American Heart Association.2009:54:98-105.

81. Positive association of serum prolactin concentrations withall – cause and cardio vascular mortality.Robin haring,Nete friedrich,henry volzke, Ramachandran S,Vasan ,Stephen B,Felix ,Marcus Dorr, Henriette E,Meyer Zu,Schwabedissenm,Matthias Nauck and Henry Wallaschofski.European heart journal .july 9 ,2012.

82. Sexual hormone abnormalities in male patients with renal failure.Schmidt A,Luger A,Horl WH,Nephrol Dial Transplant 2002:17:348-356.

83. The hypothalamic – pituitary axis in men and women with chronic kidney disease.Holley JL,Adv Chronic Kidney Dis 2004:11:337-341.

PROFORMA

A STUDY ON SERUM PROLACTIN LEVELS IN CKD PATIENTS &IT'S CORRELATION WITH CORONARY ARTERY HEART DISEASE

NAME: **AGE:**

SEX: **IP NO:**

History Of:

Periorbital oedema

Reduced urine output

Pedal oedema,

Difficulty in breathing

Headache

Seizures

Current pregnancy

Chronic Liver Disease

Hypothyroidism

Seizure disorder

Chronic drug intake

Chest wall surgery

Any surgery on the breast

H/O Galactorrhoea

Trauma

Menstrual history

Examination:

Anemia

Clubbing

Cyanosis

Jaundice

Pedal oedema

Lymphadenopathy

Vital signs: Pulse rate Blood pressure:

Cardiovascular system: Pericardial rub

Pericardial effusion

Respiratory system: Pleural rub / Effusion/ Pneumonitis

Abdomen : Hepatomegaly/Ascites

Central Nervous System: Focal neurological deficit

Investigations:

Complete Blood count

ESR

Peripheral smear study

Blood sugar – Fasting, 2 hours postprandial

HbA1C

Blood Urea

Serum Creatinine

Serum electrolytes

Lipid Profile

LFT

Chest x-ray

ECG

HbsAg

HCV

HIV

USG Abdomen

ECHO

Fasting Serum Prolactin Level:

S. No	I.P.Number	Age	Sex	Symptom Duration	SHT	T2 DM	DLM	Renal Parameters		Creatinine Clearence ml/min	USG Abdomen	ECG	ECHO	Serum prolactin [ng/ml]
								Urea	Creatinine		Evidence for CKD	Evidence for CAHD	Evidence for CAHD.	
1	39746	55	M	3 years	P	***P***	P	80	3.1	23	Present	**Present**	**Present**	**32.94**
2	33156	50	M	2 Years	P	A	P	135	11.0	5.8	Present	Absent	Absent	**65.97**
3	33695	48	M	3 Years	P	***P***	A	98	4.2	18.25	Present	Absent	Absent	10.11
4	39829	41	M	1 Year	P	A	P	170	18.4	5.5	Present	**Present**	**Present**	**37.86**
5	40209	61	M	3 Years	P	***P***	A	82	2.0	27.43	Present	Absent	Absent	9.28
6	34509	37	M	2 Years	P	***P***	P	132	11.4	7.53	Present	Absent	Absent	19.46
7	39753	45	M	3 years	P	A	A	66	2.9	22.75	Present	Absent	Absent	**23.66**
8	40300	34	M	6 months	P	A	A	45	1.6	46	Present	**Present**	**Present**	**53.23**
9	40251	64	M	1 Year	P	A	A	130	10.8	5.86	Present	Absent	Absent	**31.41**
10	36380	53	M	2 Years	P	A	A	66	2.4	25.17	Present	Absent	Absent	**45.58**

S. No	I.P.Number	Age	Sex	Symptom Duration	SHT	T2DM	DLM	Renal Parameters		Creatinine Clearence	USG Abdomen	ECG	ECHO	Serum Prolactin [ng/ml]
								Urea	Creatinine		Evidence for CKD	Evidence for CAHD	Evidence for CAHD	
11	38664	47	M	4 Years	P	***P***	A	78	4.4	15	Present	**Present**	**Present**	**80.49**
12	32323	50	M	3 Years	P	A	**P**	120	9.0	8.33	Present	Absent	Absent	**25.48**
13	39733	55	M	8 Years	P	***P***	P	90	3.3	17.89	Present	Absent	Absent	9.2
14	39702	29	F	5 Years	P	A	A	102	7.0	11.01	Present	Absent	Absent	15.02
15	40244	55	M	5 Years	P	**P**	A	105	7.3	9.7	Present	**Present**	**Present**	**55.34**
16	39846	60	M	7 Years	P	***P***	A	108	6.8	8.17	Present	Absent	Absent	12.66
17	39859	55	M	7 Years	P	A	A	50	1.6	29.51	Present	Absent	Absent	10
18	40683	38	M	3 Years	P	A	A	69	2.6	27	Present	**Present**	**Present**	**24.33**
19	40662	50	M	2 Years	P	A	A	138	7.6	9.87	Present	Absent	Absent	**29.14**
20	39875	65	M	7 Years	P	A	**P**	50	1.5	27.78	Present	Absent	Absent	7.26

S. No	I.P.Number	Age	Sex	Symptom Duration	SHT	T2DM	DLM	Renal Parameters		Creatinine Clearance	USG Abdomen	ECG	ECHO	Serum Prolactin [ng/ml]
								Urea	Creatinine		Evidence for CKD	Evidence for CAHD	Evidence for CAHD	
21	39172	54	M	2 Years	P	A	P	92	3.4	17.57	Present	Present	Present	36.93
22	35342	46	M	6 Years	P	P	A	90	6.0	13.06	Present	Absent	Absent	5.73
23	36321	49	M	6 Years	P	A	A	162	15.9	4.77	Present	Absent	Absent	91.1
24	40339	53	M	6 Years	P	A	P	120	7.0	8.63	Present	Absent	Absent	13.29
25	39026	58	M	3Years	P	P	A	105	8.4	8.13	Present	Present	Present	34.44
26	41478	60	M	4 Years	P	P	A	80	4	16.67	Present	Absent	Absent	110.1
27	40579	33	M	7 Years	P	P	P	62	2.0	29.72	Present	Absent	Absent	4.27
28	28171	60	M	2 Years	P	A	A	100	2.2	25	Present	Present	Present	45.28
29	23464	48	M	6 Years	P	A	A	102	7.0	10.95	Present	Present	Present	21.94
30	41169	60	M	8 Years	P	A	A	99	4.0	19.44	Present	Absent	Absent	8.2

S. No	I.P.Number	Age	Sex	Symptom Duration	SHT	T2 DM	DLM	Renal Parameters		Creatinine Clearence	USG Abdomen	ECG	ECHO	Serum Prolactin [ng/ml]	Serum Prolactin [ng/ml]
								Urea	Creatinine		Evidence for CKD	Evidence for CAHD	Evidence for CAHD		
31	36572	50	F	5 Years	P	***P***	A	116	8.2	9.07	Present	**Present**	**Present**	8.24	8.24
32	37484	54	M	5 Years	P	A	A	126	8.6	8.33	Present	**Present**	**Present**	**126.59**	**126.59**
33	40586	64	M	6 Years	P	A	P	72	2.7	22.02	Present	Absent	Absent	7.47	7.47
34	39276	55	M	3 Years	P	***P***	A	120	4.5	13.12	Present	**Present**	**Present**	**22.05**	**22.05**
35	40251	64	M	5 Years	P	***P***	A	140	11.2	6.6	Present	Absent	Absent	**61.56**	**61.56**
36	36275	50	M	5 Years	P	A	P	122	8.8	8.52	Present	Absent	Absent	**39.66**	**39.66**
37	38133	44	M	4 Years	P	A	A	112	9.9	8.08	Present	**Present**	**Present**	**23.17**	**23.17**
38	35702	60	M	6 Years	P	A	A	120	7.7	7.22	Present	Absent	Absent	5.94	5.94
39	39376	48	M	7 Years	P	***P***	P	142	8.5	9.02	Present	Absent	Absent	7.6	7.6
40	31568	43	M	5 Years	P	A	A	132	9.4	8.6	Present	**Present**	**Present**	**85.83**	**85.83**

S. No	I.P.Number	Age	Sex	Symptom Duration	SHT	T2DM	DLM	Renal Parameters		Creatinine Clearence	USG Abdomen	ECG	ECHO	Serum Prolactin [ng/ml]
								Urea	Creatinine		Evidence for CKD	Evidence for CAHD	Evidence for CAHD	
41	34581	50	M	2 Years	P	A	A	150	14.4	5.5	Present	present	Present	57.82
42	35676	60	M	6 Years	P	P	A	68	2.4	23.15	Present	Absent	Absent	11.17
43	36093	40	M	7 Years	P	A	P	120	6.0	11.57	Present	Absent	Absent	12.21
44	55342	43	F	3 Years	P	A	A	90	3.8	12.0	Present	Present	Present	103.43
45	36214	48	M	3 Years	P	A	A	102	5.0	12.78	Present	Absent	Absent	4.28
46	35097	62	F	4 Years	P	P	A	120	3.2	11.0	Present	Present	Present	64.96
47	34154	40	M	7 Years	P	A	P	156	12.1	6.89	Present	Absent	Absent	24.4
48	36378	53	M	3 Years	P	A	P	116	8.5	7.11	Present	Absent	Absent	13.6535
49	35386	62	M	6 Years	P	P	A	60	2.8	19.35	Present	Absent	Absent	5.62
50	35550	70	M	8 Years	P	A	A	96	4.5	10.8	Present	Absent	Absent	6.49

ABBREVIATIONS USED IN MASTER CHART

S.NO	**SERIAL NUMBER**
I.P.NUMBER	**IN PATIENT NUMBER**
SHT	**SYSTEMIC HYPERTENSION**
T2DM	**TYPE 2 DIABETES MELLITUS**
DLM	**DYSLIPIDEMIA**
USG ABDOMEN	**ULTRASONOGRAM ABDOMEN**
CKD	**CHRONIC KIDNEY DISEASE**
CAHD	**CORONARY ARTERY HEART DISEASE**
ECG	**ELECTROCARDIOGRAM**
ECHO	**ECHOCARDIOGRAM**
P	**PRESENT**
A	**ABSENT**

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .R.K.CHANDRAMOULI,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :
Date :

Signature of participant

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :

நாள்பட்ட சிறுநீரக நோய் (Chronic Kidney Disease) எனும் நோயினால் பாதிக்கப்பட்ட நோயாளிகளின் இரத்தத்தில் உள்ள புரோலாக்டின் (Prolactin) என்ற ஹார்மோன் அளவையும் மற்றும் இரத்தத்தில் உள்ள புரோலாக்டின் அளவுக்கும் மாரடைப்பு ஏற்படுவதற்கான வாய்ப்பை (Coronaryartery Disease) கண்டறிவதற்கான ஆய்வு.

பெயர்	:	தேதி	:
வயது	:	எண்	:
இனம்	:	ஆராய்ச்சி சேர்க்கை எண்:	

இந்த ஆராய்ச்சியின் விவரங்களும் அதன நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது எனபதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகள் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :