بسم الله الرحمن الرحيم

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Evaluation of Tri-iodothyronin and Thyroxine among Patients with Renal Failure in shendi Locality

A thesis submitted for partial fulfillment of the M.S.c Degree in Clinical Chemistry

By

Tagwa Hessiun Modather Abdalgader

MS.c (Shendi University)

Supervisor

Dr Abd Elwahab Abdien Saeed

PHD in Clinical Chemistry

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الآيـــة

قال تعالى:

﴿ سَلَامٌ هِيَ حَتَّىٰ مَطْلَعِ الْفَجْرِ ﴾

سـورة القـدر – الآيـة (٥)

Dedeication

I dedicate this research to my mother, my father,

I dedeicate to my brothers, sisters

and to my husband and my sons

(Mohammed and Mustafa)

Also I am very grateful to my friend and family for their good humour and support throughout the production of this project.

Acknowledgment

All thank to Allah from the start to the end...

And pray for Prophet Mohammed peace is upon him

I would like to acknowledge the contribution of my supervisor:

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Who guide me throughout my way and helped me to make this research as accurate and useful as possible.

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My thank also extend to my college and my teachers.

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List of Abbreviation

Abbreviation	Meaning
ACE	Angiotensin-Converting Enzyme
ACTH	Adreno Cortico Trophic Hormone
ADH	Anti Diuretic Hormone
AKI	Acute Kidney Injury
anti-Tg	anti-Thyroglobulin
Anti-TPO	Anti-Thyroid Peroxidase
ARBs	Angiotensin II Receptor Blockers
ATN	Acute Tubular Necrosis
ATPase	Adenosine Tri Phosphatase
CKD	Chronic Kidney Disease
DI	Di Iodotyrosine
ECF	Extra Cellular Fluid
f T3	free Triiodothyronine
f T4	free Thyroxine
FSH	Follicle-Stimulating Hormone
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
HD	Hemodialysis
HDF	Hemo DiaFiltration
HF	HemoFiltration
I^-	Iodide
IGT	Impaired Glucose Tolerance
JGA	Juxta Glomerular Apparatus
KDIGO	Kidney Disease Improving Global Outcomes
LDL	Low Density Lipoprotein

LH	Luteinizing Hormone
MCV	mean corpuscular volume
MI	Mono Iodotyrosine
NTI	Non Thyroidal Illness
PD	Peritoneal Dialysis
P_{GCap}	Glomerular-Capillary hydrostatic Pressure
RRT	Renal Replacement Therapy
rT3	reverse T3
SCH	Sub Clinical Hypothyroidism
SHBG	Sex Hormone-Binding Globulin
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine Binding Globulin
TG	ThyroGlobulin
TPO	Thyroid Peroxidase
TPOAbs	anti Thyroid Peroxidase Antibodies
TRH	Thyrotrophin Releasing Hormone
TSH	Thyroid Stimulating Hormone
TSI	Thyroid-Stimulating Immunoglobulin
tT3	*Total Triiodothyronine*
tT4	*Total Thyroxine*
TTF-1	Thyroid Transcription Factor-1
TTF-2	Thyroid Transcription Factor-2
TTR	Transthyretin

Abstract

This is descriptive, prospective analytical study which conducted in Shendi town to determine the thyroid hormones (T3 and T4) level in renal disease patients during the period from March - July 2018.

Total of 40 heparenized sample were collected from renal diseases patients with different age as test group and 30 heparenized plasma were collected from healthy persons as control group.

The collected heparenized plasma tested for measure of thyroid hormones level (T3 and T4) using immunoassay method. The result analyzed statistically by using SPSS, and showed that mean of thyroid hormone levels:

Mean of test T3 equal 1.55nmol/l and mean of control 1.78nmol/l, with P. value of 0.016, and mean of S.T4 was 79.68nmol/l and mean of control 96.11nmol/l, with P. value of 0.01 that means there was statistically significant decrease in thyroid hormone levels in test group, as shown in tables (4.1, 4.2) may be due to the effects of uremia on thyroid function at several levels: (a) subnormal pituitary TSH response to TRH; (b) possible intrathyroidal abnormalities as suggested by slightly decreased TT4 and high incidence of goiter; and (c) abnormal peripheral generation of T3 from T4.

Statistical analysis shows that there significant variation in thyroid hormones (T3 andT4) level among the age (decrease with increase in age), as shown in table (4.3) Statistical analysis show insignificant variation in thyroid hormones level with other factors example gender types of diets and duration of renal diseases in our study. Our results agree with study conducted by Victoria Sy Lim, Victor S. Fang, Adrian I. Katz, and Samuel Refetoff.

ملخص البحث

هذه دراسة وصفية تحليلية مستقبلية أجريت في مدينة شندي لتحديد مستوي هرمونات الغدة الدرقية (T3 و T4)في مرضى الكلى، خلال الفترة من مارس – يوليو عام ٢٠١٨ تم جمع ٤٠عينة بلازما من مرضي الكلي من أعمار مختلفة كمجموعة إختبار وتم جمع ٣٠ عينة بلازما من أصحاء كمجموعه ضابطة . تم إحتبار البلازما التي تم جمعها لقياس مستوي هرمونات الغدة الدرقية (T3 و T4) باستخدام طريقة مناعية و تم تحليل النتائج إحصائيا بإستخدام SPSS وأظهرت النتيجة أن متوسط معدل هرمونات الغدة الدرقية :

متوسط مستوى T3 يساوي ١,٥٥nmol/l ومتوسط العينة الضابطة ١,٧٨nmol/l و القيمة الاحتمالية 0.016 ومتوسط الإختبار T4 يساوي٧٩,٦٨ nmol/l ومتوسط العينة الضابطة 96.11nmol/l, والقيمة الاحتمالية 0.01 وهذا يعني أن هنالك تاثير ذو دلالة إحصائية.

يظهر التحليل الإحصائي أن هناك إختلاف كبير بين أمراض الكلي والأصحاء في مستوي هرمونات الغده الدرقية (T3 و T4) .

يظهر التحليل الإحصائي أن هنالك تباينا" كبيرا" في مستوي هرمونات الغدة الدرقية (T3 و T4) بين الأعمار (تقل مع زيادة العمر) .

ويظهر التحليل الإحصائي أنه لا يوجد تباين في مستوي هرمونات الغدة الدرقية مع عوامل أخري مثل الجنس ونوع الطعام والفترة الزمنية لمرض الكلي في هذه الدراسة. هذه النتائج توافقت مع دراسة اخرى اجريت بواسطة Victoria Sy Lim, Victor S. Fang, Adrian . I. Katz, and Samuel Refetoff

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1.1 Introduction

The kidneys are paired retroperitoneal organs each comprising about 1 million nephrons, which act as independent functional units. They have multiple physiological functions, which can be broadly categorized as the excretion of waste products, the homeostatic regulation of the ECF volume and composition, and endocrine. In order to achieve these functions, they receive a rich blood supply, amounting to about 25% of the cardiac output. The excretory and homeostatic functions are achieved through filtration at the glomerulus and tubular reabsorption. The glomeruli act as filters which are permeable to water and low molecular weight substances, but impermeable to macromolecules.

This impermeability is determined by both size and charge, with proteins smaller than albumin (68 kDa) being filtered, and positively charged molecules being filtered more readily than those with a negative charge. The filtration rate is determined by the differences in hydrostatic and oncotic pressures between the glomerular capillaries and the lumen of the nephron, by the nature of the glomerular basement membrane and by the total glomerular area available for filtration.

Thyroid hormones are essential for normal growth, development and metabolism, and their production is tightly regulated through the hypothalamic–pituitary– thyroid axis. [(1)]

The total glomerular area available reflects the total number of functioning nephrons. The total volume of the glomerular filtrate amounts to about 170 L/day (12 times the typical ECF volume), and has a composition similar to plasma except that it is almost free of protein.

The renal tubules are presented with this volume of water, most of which needs to be reabsorbed, containing a complex mixture of ions and small molecules, some of which have to be retained and some in a regulated manner; small amounts of small proteins which are reabsorbed and catabolised; and metabolic waste products such as urea, creatinine and sulphate ions, which are excreted. The proximal convoluted tubule is responsible for the obligatory reabsorption of

much of the glomerular filtrate, with further reabsorption in the distal convoluted tubule being subject to homeostatic control mechanisms. In the proximal tubule, energy dependent mechanisms reabsorb about 75% of the filtered Na+ and all of the K+, HCO3, amino acids and glucose, with an isosmotic amount of water. In the ascending limb of the loop of Henle, Cl− is pumped out into the interstitial fluid, generating the medullary hypertonicity on which the ability to excrete concentrated urine depends. This removal of Na+ and Cl− in the ascending limb results in the delivery to the distal convoluted tubule of hypotonic fluid containing only 10% of the filtered Na+ and 20% of the filtered water. The further reabsorption of Na+ in the distal convoluted tubule is under the control of aldosterone, and generates an electrochemical gradient which promotes the secretion of K+ and H+.The collecting ducts receive the fluid from the distal convoluted tubules and pass through the hypertonic renal medulla. In the absence of vasopressin, the cells lining the ducts are impermeable to water, resulting in the excretion of dilute urine. (1)

Thyroid disease is common, particularly in women, and the prevalence rises with age such that around 10% of the population over 65 years of age may have some abnormality in thyroid function. Although primary diseases of the thyroid gland are the most common, pituitary disease and the use of certain drugs can also give rise to thyroid dysfunction. Once diagnosed, thyroid disease is easily treated, with an excellent long term outcome for most patients. Several laboratory tests may be affected by changes in thyroid status. It is particularly important to exclude abnormalities in thyroid function in patients with newly diagnosed diabetes, and also those with hypercholesterolaemia. Changes in sex hormonebinding globulin (SHBG) concentration can lead to marked changes in the free hormone concentration of testosterone. (1)

1.2 Justification

The renal disease is more common cause of death in this days and the one of its risk factors the change of serum level of thyroid hormones, recently there is no researches was conducted in Shendi locality so I want to determine the level of thyroid hormones in renal diseases.

1.3 Objectives

1.3.1 General objective

Evaluate serum thyroid hormones level (tri-iodothyronin and thyroxine) in renal diseases patients.

1.3.2 Specific objectives

1. To evaluate the thyroid hormones (tri-iodothyronin and thyroxine) in renal disease patients and compare it with control group.
2. To determine the effect of age of test group on thyroid hormones (tri-iodothyronin and thyroxine).
3. To estimate the effect of gender on thyroid function tests (tri-iodothyronin and thyroxine).
4. To determine the effect of disease duration on thyroid hormones levels (tri-iodothyronin and thyroxine).

Chapter Two

Literature Review

2. Literature review

2.1 The kidney

The kidneys form a paired organ system located in the retroperitoneal space. They extend from the level of the lower part of the 11th thoracic vertebra to the upper portion of the 3rd lumbar vertebra, with the right kidney situated slightly lower than the left. The adult kidney is about 12 cm long and weighs about 150 g. The kidneys have both sympathetic and parasympathetic nerve supplies, whose function appears to be predominantly associated with vasomotor activity. The renal lymphatic drainage includes fine lymphatics in the glomerulus, some in close proximity to the juxtaglomerular apparatus (JGA†), which are associated with removal of material from the glomerular mesangial cells. (2)

2.1.1 Kidney physiology

The nephron is the structural and functional unit of the kidney. Each adult kidney contains around one million nephrons. The nephron utilizes four processes to alter the blood plasma which flows to it: filtration, reabsorption, secretion, and excretion. Via one or more of these mechanisms, the kidney participates in the control of the volume of various body fluid compartments, fluid osmolality, acid-base balance, various electrolyte concentrations, and removal of toxins. Filtration occurs in the glomerulus: one-fifth of the blood volume that enters the kidneys is filtered. Examples of substances reabsorbed are solute-free water, sodium, bicarbonate, glucose, and amino acids. Examples of substances secreted are hydrogen, ammonium, potassium and uric acid. The kidneys also carry out functions independent of the nephron. For example, they convert a precursor of vitamin D to its active form – calcitriol – and synthesize the hormones erythropoietin and renin. (3)

The glomeruli The glomerulus is formed from a specialized capillary network. Each capillary develops into approximately 40 glomerular loops around 200 μm in size and consisting of a variety o different cell types supported on a specialized basement membrane there are endothelial and epithelial cells that act in concert with the specialized glomerular basement membrane to form the

glomerular filtration barrier. The glomerular capillaries are supported by a network of mesangial cells and mesangial matrix that act as connective tissue or the glomerular apparatus. The basement membrane forms the main size discriminant barrier to protein passage into the tubular lumen. (4)

The proximal convoluted tubules also in the cortex, receive filtrate from the glomerular spaces. Convolution increases the tubular length and therefore contact between the luminal fluid and the proximal tubular cells. (3)

The loops of Henle extend down into the renal medulla and ascend again after forming the loop. The pars recta drains into the descending thin limb of the loop of Henle, which after passing through a hairpin loop becomes first the ascending thin limb and then the thick ascending limb. At the end of the thick ascending limb, there is a cluster of cells known as the macula densa. The main role o the loop of Henle is to provide the ability to generate concentrated urine, hypertonic with respect to plasma. (4)

The distal convoluted tubules situated in the cortex, are important for fine adjustment of luminal fluid. They lie near the afferent arterioles, with the juxtaglomerular apparatus between them. The enzyme renin is produced by the latter and its release is controlled by local blood flow. (3)

The collecting ducts start as the distal tubules lead down into the medulla and end by opening into the renal pelvis. The modified fluid from the original filtrate flows from the collecting ducts into the renal tract.

Normal function of the kidneys depends on the following:

1. An adequate blood supply, which under normal circumstances is about 20 per cent of the cardiac output, flowing through the kidneys,
2. Normal secretion and feedback control of hormones acting on the kidney
3. The integrity of the glomeruli and the tubular cells. (3)

Juxtaglomerular Apparatus where the ascending loop of Henle passes very close to the Bowman capsule of its own nephron, the cells of the tubule and the afferent arteriole show regional specialization. The tubule forms the macula densa and the arteriolar cells are filled with granules (containing renin) and are

innervated with sympathetic nerve fibers. This area is called the juxtaglomerular apparatus (JGA). The JGA plays an important part in maintaining systemic blood pressure through regulation of the circulating intravascular blood volume and sodium concentration. [4]

2.1.2 Blood Supply

In most cases, each kidney receives its blood supply from a single renal artery derived from the abdominal aorta. However, multiple renal arteries occur commonly. The renal artery divides into posterior and anterior elements, and ultimately into the afferent arterioles, which expand into the highly specialized capillary beds that form the glomeruli, these capillaries then rejoin to form the efferent arteriole that then forms the capillary plexuses and the elongated vessels (the *vasa recta*) that pass around the remaining parts of the nephron, the proximal and distal tubules, the loop of Henle, and the collecting duct, providing oxygen and nutrients and removing ions, molecules, and water, which have been reabsorbed by the nephron. The efferent arteriole then merges with renal venules to form the renal veins, which merge into the inferior vena cava.

In adults, the kidneys receive approximately 25% of the cardiac output, about 90% of which supplies the renal cortex, maintaining the highly active tubular cells. Maintenance of renal blood flow is essential to kidney function, and a complex array of intrarenal regulatory mechanisms ensure that it is maintained across a wide range of systemic blood pressures. The renal glomerular perfusion pressure is maintained at a constant 45 mm Hg across systemic pressures between 90 and 200 mm Hg. [3]

2.1.3 Kidney functions

The kidneys regulate and maintain the constant optimal chemical composition of the blood and the interstitial and intracellular fluids throughout the body—the internal milieu—through integration of the major renal functions— namely filtration, reabsorption, and excretion. Mechanisms of differential reabsorption and secretion, located in the tubule of a nephron, are the effectors of regulation.[3]

Excretory and Reabsorptive Functions

The *excretory function* of the kidneys serves to rid the body of many end products of metabolism and of excessive inorganic substances ingested in the diet. Waste products include the non protein nitrogenous compounds urea, creatinine, and uric acid; a number of other organic acids, including amino acids, are excreted in small quantities. Daily intake of water is also variable and may, on occasion, greatly exceed the requirements of the body. Under such circumstances, water becomes additional waste material requiring excretion. To achieve excretion of metabolic wastes and ingested surpluses without disrupting homeostasis, the kidneys must exercise both their *excretory* and *reabsorptive* functions.

Urine is defined as a fluid excreted by the kidneys, passed through the ureter, stored in the bladder, and discharged through the urethra. In health, it is sterile and clear and has an amber color, a slightly acid pH (approximately 5.0–6.0), and a characteristic odor. In addition to dissolved compounds, it contains a number of cellular fragments and complete cells, derived from normal turnover of tubular cells, casts, and crystals (formed elements). Urinary casts are cylindrical proteinaceous structures formed in the distal convoluted tubule and collecting ducts, which dislodge and pass into the urine, where they can be detected by microscopy.[3]

Regulatory Function Electrolyte Homeostasis

A complex interplay has been noted between the tubular transport systems regulating individual electrolytes. For simplicity, we have considered each electrolyte individually and have restricted our discussion to the systems of major physiologic, pharmacologic, and pathologic significance. [3]

Sodium reabsorption is required for the reabsorption of water and many solutes. The proximal tubule is highly permeable to sodium, and the net flux of reabsorption from the tubular lumen is achieved against a high backflux, particularly from paracellular (transport that occurs between tubular epithelial cells by passive diffusion or solvent drag) movement.

Approximately 60% of filtered sodium is reabsorbed in the proximal tubule in an energy-dependent manner, driven by basolateral Na, K-ATPase pumps. [1]

Potassium approximately 90% of daily potassium loss occurs via renal elimination. Potassium is freely filtered across the glomerulus and normally is almost completely reabsorbed in the proximal tubule. However, most regulatory mechanisms affect the loop of henle, the distal tubule, and the collecting duct. Indeed, urinary losses can exceed filtered load, indicating the importance of distal secretion.

Determinants of urinary potassium loss are dietary intake of potassium and plasma potassium concentration, acid-base disturbances (acidosis reduces potassium secretion and vice versa), circulating vasopressin concentration (vasopressin increases potassium loss), tubular flow rate. [5]

Chloride approximately 60% of chloride is reabsorbed in the proximal tubule. In the early part of the proximal tubule, avid reabsorption of sodium in combination with glucose and amino acids occurs, creating a lumen-negative potential difference. The negative potential difference drives chloride reabsorption by diffusion through the paracellular pathway. Preferential reabsorption of glucose, amino acids, and bicarbonate in association with sodium in the early proximal tubule causes an increase in the luminal chloride concentration. This high chloride composition heralds the second phase of proximal chloride (and sodium) reabsorption: passive diffusion of sodium chloride via the paracellular pathway, and active reabsorption involving several antiporter systems, by which chloride is exchanged for secretion of other anions (eg, bicarbonate, formate, and oxalate). [6]

Calcium approximately 98% of filtered calcium is reabsorbed: 65% to 75% in the proximal tubule (via a paracellular pathway), 20% to 25% in the thick ascending limb of the loop of Henle, 10% in the distal tubule, and, finally, small amounts in the collecting ducts. Calcium reabsorption is predominantly a passive process linked to active sodium reabsorption. [7]

Phosphate reabsorption of phosphate occurs predominantly in the proximal tubule and is mediated by a secondary active transport mechanism. Sodium phosphate transporter is electrogenic (ie, involves the inward flux of a positive charge), with three sodium ions and one phosphate ion (preferentially divalent) being transferred. Also involving increased transcription of the protein. [7]

Bicarbonate and Hydrogen Ion the kidney plays a central role in the maintenance of acid-base homeostasis through reabsorption of filtered bicarbonate and secretion of ammonium and acid.

Water Homeostasis approximately 180L glomerular filtrate is formed each day. The unique physiology of the kidney enables approximately 99% of this to be reabsorbed in the production of urine with variable osmolality (between 50 and 1400 mOsmol766/kg H_2O at extremes of water intake). Plasma membranes of all mammalian cells are water permeable but to variable degrees. In the kidney, different segments of the nephron show differing permeability to water, enabling the body to both retain water and produce urine of variable concentration. Water reabsorption occurs both isosmotically, in association with electrolyte reabsorption in the proximal tubule, and differentially, in the loop of Henle, distal tubule, and collecting duct in response to the action of vasopressin. Absorption of water depends on the driving force for water reabsorption (predominantly active sodium transport) and the osmotic equilibration of water across the tubular epithelium. The generation of concentrated urine depends on medullary hyperosmolality.

Urinary concentration is predominantly achieved by countercurrent multiplication in the loop of Henle.

Endocrine Function

-Erythropoietin.

-Prostaglandins and Thromboxanes.

-1, 25(OH_2) D3. [8]

Glomerular Filtration Rate the GFR is considered to be the most reliable measure of the functional capacity of the kidneys and is often thought of as indicative of the number of functioning nephrons. As a physiologic measurement, it has proved to be the most sensitive and specific marker of changes in overall renal function.

The rate of formation of glomerular filtrate depends on the balance between hydrostatic and oncotic forces along the afferent arteriole and across the glomerular filter. The net pressure difference must be sufficient not only to drive filtration across the glomerular filtration barrier but also to drive the ultrafiltrate along the tubules against their inherent resistance to flow. In the absence of sufficient pressure, the Lumina of the tubules will collapse. This balance of forces can be expressed as follows: contraction, which is thought to be the main mechanism. Net *P*GCap represents a balance between renal arterial pressure and afferent and efferent arteriolar resistance. Although an increase in arterial pressure will tend to increase *P*GCap, the magnitude of the change is modulated by differential manipulation of afferent and efferent tone, which can result in minimal change to the *P*GCap. When the renal blood flow is low, oncotic pressure can change as the plasma passes along the renal capillaries. [(9)]

2.1.4 Age and the Kidney

Kidney function varies throughout life. In utero, urine is produced by the developing fetus from about the ninth week of gestation. Nephrogenesis is complete by approximately 35 weeks' gestation, although kidney function remains immature during the first 2 years of life. The kidney of the term infant receives approximately 6% of the cardiac output, compared with 25% in adults. Renal vascular resistance is relatively high, and the low renal blood flow is particularly directed to the medulla and inner cortex. The gradual increase in renal blood flow that occurs with increasing age is directed mainly to the outer cortex and is mediated by local neurohormonal mechanisms. The GFR at birth is approximately 30mL/ min/1.73 m2. It increases rapidly during the first weeks of

life to reach approximately 70 mL/min/1.73 m2 by age 16 days. Normal adult values are achieved by age 14 years.

Tubular functions, including salt and water conservation, are also immature at birth. Birth is associated with rapid changes in kidney function, with a switch to salt and water conservation mediated by catecholamines, the renin-angiotensin system, vasopressin, glucocorticoids, and thyroid hormone. (eg, 82% of a residential home population were identified as having a GFR <60 mL/min/1.73 m2). The incidence of AKI also increases with age. [10]

2.2 Biochemistry of renal disorders

2.2.1 Pathophysiology

Despite the diverse initial causes of injury to the kidney, progression of kidney disease leading to loss of function and ultimately to kidney failure is a remarkably monotonous process characterized by early inflammation, followed by accumulation and deposition of extracellular matrix, tubulointerstitial fibrosis, tubular atrophy, and glomerulosclerosis. Proteinuria is thought to be one of the most important risk factors for progression of kidney diseases. Nephrons are also lost via toxic, anoxic, or immunologic injury that initially may occur in the glomerulus, the tubule, or both together. Glomerular damage can involve endothelial, epithelial, or mesangial cells and/or the basement membrane. [11]

Different parts of the nephrons are in close anatomical association and are dependent on a common blood supply. Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes either glomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved. [3]

Clinical and biochemical features of renal disease

Urine

- Reduced volume (oliguria).

- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.
- High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

Plasma

- High urea (uraemia) and creatinine concentrations.
- Low bicarbonate concentration, with low pH (acidosis).
- Hyperkalaemia.
- Hyperuricaemia and hyperphosphataemia.

The biochemical findings and urine output in renal disease depend on the relative contributions of glomerular and tubular dysfunction. When the GFR falls, substances that are little affected by tubular action (such as urea and creatinine) are retained. [3]

2.2.2 Acute kidney injury

The definition of AKI, endorsed by the Kidney Disease Improving Global Outcomes (KDIGO) during 2012, is the occurrence of any one of the following:

- Increase o plasma creatinine by ≥ 0.3 mg/dL (≥ 26 umol/L) within 48 hours
- Increase in plasma creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Reduction in urine output (documented oliguria < 0.5 mL/kg/h or > 6 hours). [4]

Clinical assessment of AKI should consider whether the precipitant is prerenal, intrarenal (intrinsic), or postrenal. Most commonly, AKI is caused by ischemia, which initiates a complex sequence of hemodynamic changes, endothelial injury, epithelial cell injury, and immunological mechanisms that underpin its initiation and extension. Intrinsic AKI can be caused by primary vascular, glomerular, or interstitial disorders. It is therefore important that all patients presenting with AKI undergo urinalysis to test for infection, hematuria, and proteinuria. In most cases the kidney lesion seen on histology is referred to as

acute tubular necrosis (ATN). ATN is caused by ischemic or nephrotoxic injury to the kidney. In 50% of cases of hospital-acquired AKI, the cause is multifactorial.

Although the pathogenesis is uncertain, a well-recognized clinical pattern is associated with the development of ATN, with anuria or oliguria and abnormalities indicating tubular dysfunction. [12]

Necrosis of tubular cells need not be extensive, but obstruction by tubular casts, back-leak of glomerular filtrate through gaps in the tubular epithelium caused by cellular denudation, and primary reductions in GFR caused by altered intrarenal hemodynamics, known as tubuloglomerular feedback, may occur. [13]

2.2.3 Chronic kidney disease

Chronic renal dysfunction [defined as being reduced eGFR (estimated GFR), proteinuria, haematuria and/or renal structural abnormalities of more than 90 days' duration] is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular dysfunction and the use of nephrotoxic drugs . It is common, perhaps affecting about 13 per cent of the population. Acute or chronic renal dysfunction can occur when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are given to patients with renal artery stenosis; a clue to this is an increase in plasma creatinine of about 20 per cent and/or a decrease in eGFR of about 15 per cent soon after initiation of the drug. [3]

Acid–base disturbances

The total excretion of H^+ is impaired, mainly due to a fall in the renal capacity to form NH_4. Metabolic acidosis is present in most patients, but its severity remains fairly stable in spite of the reduced urinary H^+ excretion. There may be an extra renal mechanism for H^+ elimination, possibly involving buffering of H^+ by calcium salts in bone; this would contribute to the demineralization of bone that often occurs in chronic kidney disease.

Other findings in chronic kidney disease may include impaired glucose tolerance (IGT) and raised plasma magnesium. These may need appropriate treatment, but are of no particular diagnostic significance.

Impaired renal erythropoietin synthesis contributes to the anaemia which is often present in patients with chronic kidney disease. Biosynthetic erythropoietin can be used to treat this. (1)

2.2.4 Syndromes reflecting predominant tubular damage

- Renal tubular acidosis

There is a group of conditions that primarily affect tubular function more than the function of the glomeruli. However, scarring involving whole nephrons may eventually cause chronic renal dysfunction.

Impaired function may involve a single transport system; particularly disorders associated with amino acid or phosphate transport, or may affect multiple transport systems. Conditions associated with multiple transport defects may cause renal tubular acidosis.

– Renal tubular disorders associated with a systemic metabolic acidosis because of impaired reclamation of bicarbonate or excretion of H^+.

Disorders affecting the urine-concentrating mechanism and causing nephrogenic diabetes insipidus but which rarely in themselves cause a metabolic acidosis are discussed elsewhere. (3)

Nephrotic syndrome

Nephrotic syndrome is defined as heavy proteinuria (>3 g/d), reduced serum albumin concentration, and edema. In comparison with nephritic syndrome, nephrotic patients may exhibit an otherwise bland urinary sediment with little hematuria. Nephrotic syndrome can occur at any age from neonate to elderly. Although the underlying kidney disease tends to vary with age, in all cases the lesion is within the glomerulus and is associated with damage to the specialized visceral epithelial cells, the podocytes (see earlier). Proteinuria is a consequence of a reduction in the charge-selective properties of the filtration barrier,

particularly the GBM, and of alterations in the slit diaphragms of interdigitating foot processes of adjacent podocytes. [14]

Nephritic syndrome

This disorder is characterized by rapid onset of hematuria, proteinuria, reduced GFR, and sodium and water retention, with resulting hypertension and localized peripheral edema.

Congestive heart failure and oliguria may also develop. In a number of patients with the acute nephritic syndrome, the pathologic process is related to recent group A β-hemolytic streptococcal infection of the pharynx or, less commonly, the skin. [15]

Renal canculi

Physicochemical principles govern the formation of renal stones, and are relevant to the choice of treatment aimed at preventing progression or recurrence. Stones may cause renal damage, often progressive.

The solubility of a salt depends on the product of the activities of its constituent ions. Frequently, the solubility product in urine is exceeded without the formation of a stone, provided there is no 'seeding' by particles present in urine, such as debris or bacteria, which promote crystal formation. Formation of stones can also be prevented by inhibitory substances that are normally present in the urine, such as citrate, which can chelate calcium, keeping it in solution.

People living or working in hot conditions are liable to become dehydrated, and show a greater tendency to form renal stones, as the urine becomes more concentrated. There are also several metabolic factors that can cause stones to form in the renal tract.

However, in many patients, no cause can be found to explain why stones have formed. [1]

2.2.5 Renal replacement therapy

Renal replacement therapy (RRT) includes dialysis procedures such as hemodialysis (HD), peritoneal dialysis (PD), continuous hemofiltration (HF), and continuous hemodiafiltration (HDF). These techniques are used to

temporarily or permanently remove toxic substances from the blood when the kidneys cannot satisfactorily remove them from the circulation. In addition, kidney transplantation has become an effective form of RRT. Extensive laboratory support is required by an RRT program. [16]

Dialysis

Dialysis is the process of separating macromolecules from ions and low molecular weight compounds in solution based on the difference in their rates of diffusion through a semipermeable membrane, through which crystalloids can pasreadily but colloids pass very slowly or not at all. Two distinct physical processes are involved: diffusion and ultrafiltration.

The timing of initiation of dialysis treatment is controversial and requires judgment, taking into account the treatment of metabolic consequences of advanced CKD, the comorbidities of the patient, and the accepted impact of dialysis treatment on quality of life.

Hemodialysis and Hemofiltration

HD is the method most commonly used to treat advanced and permanent kidney failure. Clinically, it is considered the default therapy that is utilized in patients unsuitable for the alternate modalities of PD and kidney transplantation.

Operationally, it involves connecting the patient to a circuit into which his or her blood flows to and from a semipermeable large surface area membrane, the hemodialyzer. After filtration to remove wastes and extra fluid, the cleansed blood is returned to the patient. This is a complicated and inconvenient therapy requiring a coordinated effort from a health care team that includes the patient, nephrologist, dialysis nurse, dialysis technician, dietitian, and others.

Peritoneal Dialysis

Peritoneal dialysis (PD) is a type of dialysis in which dialysate is passed into the patient's peritoneal cavity, with the peritoneum then employed as the dialysis membrane. It was first explored by Ganter in 1923 and initially showed poor results. A type of PD performed in ambulatory patientsduring normal activities. Peritoneal dialysis now accounts for 6.2% and 7.4% of the incident and

prevalent dialysis populations in the United States, respectively, proportions that have continued to decline over the past decade from peaks of 13% and 11% primarily as the result of an increase in HD capacity [16].

Kidney Transplantation

Kidney transplantation is the most effective form of renal replacement therapy in terms of long-term survival and quality of life. Median waiting time for a listed patient depends on his or her age. The median time to transplant for a white adult increased from 2.7 years in 1998 to 4.2 years in 2008. Although patients with kidney failure should have equitable access to kidney transplantation, currently only 23% of adult patients on dialysis in the United Kingdom are on the active renal transplant waiting list. Patients in transplanting centers are more likely to be listed than those in nontransplanting centers. [17]

Waiting time spent on dialysis has been shown to be an important factor in determining mortality. In England and Wales, 45% of patients younger than 65 years were activated on the transplant list within 1 year of starting dialysis, and 66% were activated within 5 years. Evidence suggests that the very best outcomes are achieved following preemptive (ie, before dialysis has become necessary) live donor transplants. This has led to increased emphasis on preemptive transplantation, particularly in the United Kingdom, following the National Service Framework for Renal Services, published in 2004. Since Joseph Murray in Boston performed the first successful transplant in 1954 from one twin to the other, progressive developments have occurred in this field of medicine. [18]

2.3 Endocrine:

Hormones are organic compounds produced by the endocrine system and secreted directly into the blood to act near to their site of release or at a distant organ in the body.

The endocrines system is all the hormones producing tissues.

General functions of hormones:

A. Regulation of metabolism: Hormones affect the metabolism of carbohydrate, protein, lipids and minerals, directing their synthesis, storage, mobilization and utilization according to needs.

B. Growth: The growth of bones, viscera and various types of tissues is under the control of hormones.

C. Homeostasis: Hormones help the maintenance of internal environment.

D. Behaviour: Hormones have an important role in behaviour. Fear, depression and sex behaviour are due to several natural hormonal factors.

E. Reproduction: Reproductive organs are highly sensitive to hormones.

Classification of hormones:

Hormones are classified according to chemical composition, solubility properties and mechanism of action.

A. Classification according to the chemical composition:

1. Amino acid derivatives: Such as thyroid hormones (T3, T4), epinephrine, nor epinephrine and serotonin.

2. Polypeptides: Such as pituitary hormones e.g. oxytocin, ADH, ACTH.

3. Proteins and glycoprotein&: Such as Insulin, growth hormone,

TSH, LH, FSH, parathyroid hormone, prolactin etc.

4. Steroids: Such as adrenal cortical hormones, sex hormones: estrogens, progesterone and androgens.

B. Classification according to the mechanism of action: There are 2 groups:

1. Group 1: Includes hormones that bind to the Intracellular receptors.

2. Group II: Includes hormones that bind to cell surface receptors. [19]

2.3.1 Thyroid gland

Thyroid gland is a butter y-shaped gland located in the front o the neck just above the trachea in the adult human. The fully developed thyroid gland in a human weighs approximately 15 to 20g.

However, in disease states, the gland may weigh up to several hundred grams. The thyroid is composed o two lobes with the right lobe being somewhat larger than the left lobe. The lobes are connected by the isthmus. [4]

The **thyroid follicle** or a cinus is the secretory unit of the thyroid gland. Each follicle has an outer layer for epithelial cells that enclose an amorphous material called **colloid** that is mainly composed of **thyroglobulin (TG)**. The important reactions of thyroid hormone synthesis, such as iodination and the initial phase of hormone secretion (colloid resorption into the cells), are believed to take place at or near the surface of the epithelial cells in the colloid.

The thyroid gland also contains another type of cell known as parafollicular or C cells. These cells have been shown to produce the polypeptide hormone calcitonin. These cells are conne within the follicular basement lamina or exist in clusters in the inter follicular spaces. T e thyroid gland secretes two hormones,

Thyroxine (3, 5, 3′, 5′-L-tetraiodothyronine) and triiodothyronine

(3, 5, 3′-L-triiodothyronine), which are commonly known as T4 and T3, respectively. In addition, the thyroid gland secretes very small amounts of biologically inactive 3, 3′, 5′-L-triiodothyronine (**reverse T3 [r T3]**) and minute quantities of monoiodotyrosine (MI) and di-iodotyrosine (DI), which are precursors of T3 and T4. [4]

Thyroid hormones are essential for normal growth, development and metabolism, and their production is tightly regulated through the hypothalamic–pituitary– thyroid axis.

Thyroid disease is common, particularly in women, and the prevalence rises with age such that around 10% of the population over 65 years of age may have some abnormality in thyroid function. Although primary diseases of the thyroid gland are the most common, pituitary disease and the use of certain drugs can also give rise to thyroid dysfunction. Once diagnosed, thyroid disease is easily treated, with an excellent long term outcome for most patients.

Thyroid hormone synthesis, action and metabolism

Thyroxine (T4) and small amounts of tri□iodothyronine (T3) and reverse T3 (rT3) are all synthesised in the thyroid gland by a process involving: [1]

- The thyroid gland contains many follicles, each composed of a shell of single layered cells surrounding a central space filled with glycoprotein called: thyroglobulin (TG).
- Thyroglobulin contains about 150 tyrosine residues.
- Iodide ions (1^-) can be taken up by thyroid cells and oxidized into higher value state (positive ions, ($I^•$). This needs H: z02 and thyroid peroxidase enzyme.
- I• is then incorporated into the tyrosine residues of TG.
- The resulting monoiodotyrosine and di-iodotyrosine residues react together to give one of the following compounds:

a. Tetraiodothyronine [thyroxin, T4].

b. Triiodothyronine [T3].

Reverse triiodothyronine [rT 3].

- Both T3 and T4 are biologically active, while rT3 is biologically inactive.
- Enzyme hydrolysis of thyroglobulin releases free T3 and T4 into the plasma.[20]

Plasma transport and cellular action

Thyroid hormones are transported in plasma almost entirely bound, reversibly, to plasma proteins.

Thyroxine binding globulin (TBG) is the major binding protein, binding about 70% of plasma T4 and 80% of plasma T3. Transthyretin (also called thyroxin binding pre albumin) and albumin also bind thyroid hormone such that more than 99.8% of thyroid hormones circulate bound to these three proteins.

Approximately 0.05% of plasma T4 and 0.2% of plasma T3 are free (i.e. unbound to protein). Only the free fractions can cross the cell membrane and affect intracellular metabolism. After binding to high affinity binding sites on the plasma membrane, the hormones are actively transported into cells by specific energy dependent transporters. In the cell T4 is metabolized to T3, which then binds to specific nuclear receptors that in turn activate T3 responsive

genes. These gene products modify a wide range of cell function including basal metabolic rate and the metabolism of lipids, carbohydrates and proteins. [1]

2.3.2 Regulation of thyroid function

The most important regulator of thyroid homeostasis is TSH (or thyrotrophin. The production of TSH is controlled by a stimulatory effect of the hypothalamic tripeptide, TRH (or thyroliberin), mediated by a negative feedback from circulating FT3 and FT4. It is thought that the hypothalamus, via TRH, sets the level of thyroid hormone production required physiologically, and that the pituitary acts as a 'thyroid stat' to maintain the level of thyroid hormone production that has been determined by the hypothalamus. Dopamine, somatostatin and glucocorticoids also appear to be involved in inhibiting the release of TSH, and these agents together with the interleukins may be important modifiers of TSH release in nonthyroidal illness (NTI). [1]

Thyroglobulin

Thyroglobulin (TG) is a large thyroid-specific dimeric glycoprotein. It is the major constituent of thyroid lumen, where its concentration is approximately 300 g/L. The mature protein has 2749 amino acid residues, including 66 tyrosines.

Although 10 to 15 of these tyrosyl residues can be iodinated, T4 production occurs only at sites 5, 1291, and 2554. T3 formed at 2747. The protein is extensively glycosylated, being 10% by weight carbohydrate. The 48-exon gene encoding TG contains several thyroid specific promoters (TTF-1, TTF-2) in common with the *TPO* gene, with which it shares considerable homology. TSH is the major regulator of protein synthesis. TG acts as both the scaffold and a storage depot for thyroid hormone. [21]

Thyroid Peroxidase

Thyroid peroxidase is a 933-residue heme-containing glycoprotein.

It is located at the apical membrane of the follicular cell with the active site accessible to the follicular lumen. The enzyme catalyses the oxidation of iodide by hydrogen peroxide, and in the presence of TG, iodinates and couples tyrosine

residues. Similar to TG, the synthesis of TPO is regulated by TSH. The mechanism of iodination and iodo-thyronine coupling is not fully elucidated; it is likely to involve oxidation of TPO by hydrogen peroxidase and the generation of iodine radical from iodine that can then react with the tyrosine to form mono-iodotyrosine and, subsequently, di-iodotyrosine. [22]

Circulating Thyroid Hormone–Binding Proteins

Thyroid hormones are extensively protein bound in plasma, with only 0.03% of total T4 (tT4) and 0.3% of total T3 (tT3) in plasma being circulating free or unbound. The three major hormone binding proteins are TBG, TTR, and albumin. TBG has the highest affinity for T4 and binds 75% of plasma T4. TTR binds 20% and albumin 5%. Small amounts of T4 are also bound by lipoproteins, immunoglobulins, and some plasma serpin protease inhibitors. As thyroid hormone enters target cells unbound, the free fraction of hormone in the plasma best represents the biologic activity of the thyroid hormones, the total amount being largely determined by the concentrations of binding proteins.

The function of thyroid-binding proteins is somewhat enigmatic because both naturally occurring mutations and knockout animal models do not have an obvious phenotype. [23]

Iodine and thyroid disorders

Iodine (or iodide [I-] in its ionized form) is a trace element and an essential nutrient. Iodine is an indispensable component of the thyroid hormones T3 and T4, respectively.

These hormones, together with the thyronamines, are the only iodine-containing hormones in vertebrates. Without iodine, there is no biosynthesis of thyroid hormones. Thus, thyroid function requires an adequate supply of iodine to the thyroid gland. [24]

Iodine Deficiency

Both deficient and excessive intakes of iodine can impair thyroid function. The clinical presentations of iodine deficiency are largely age dependent. In fetuses, deficiency may cause abortion, stillbirth, and congenital anomalies, and in

neonates, deficiency may cause infant mortality and endemic cretinism. In children and adolescents, deficiency may cause impaired mental function, delayed physical development. In adults, deficiency may cause impaired cognitive function, reduced work productivity, thyroid autoimmunity, toxic nodular goiter, and hyperthyroidism. In all ages, goiter is the most visible sign of iodine deficiency but is not specific to it. [25]

Iodine Excess

Thyroid dysfunction may occur in vulnerable patients if exposed to excess iodine. These patients include those with preexisting thyroid disease, older adults, pregnant and lactating women, fetuses, and neonates. Because iodine is present in medications, supplements, and iodinated contrast agents in much higher concentrations than are found in naturally occurring foods, iodine excess can result in adverse thyroidal effects after only a single exposure to these substances.

Excess dietary iodine intake in pregnant and lactating women in iodine-replete areas may lead to an increase in plasma TSH concentrations and thus to SCH.[26]

2.2.3 Action of thyroid hormones

Thyroid hormones affect many metabolic processes, increasing oxygen consumption. They bind to specific receptors in cell nuclei and change the expression of certain genes. Thyroid hormones are essential for normal growth, mental development and sexual maturation and also increase the sensitivity of the cardiovascular and central nervous systems to catecholamines, thereby influencing cardiac output and heart rate.

Control of thyroid-stimulating hormone secretion

Thyroid-stimulating hormone stimulates the synthesis and release of thyroid hormones from the thyroid gland. Its secretion from the anterior pituitary gland is controlled by thyrotrophin-releasing hormone (TRH) and circulating concentrations of thyroid hormones. [3]

Effects of thyroid hormones in the control of thyroid stimulating hormone secretion

Thyroid hormones reduce TSH secretion by negative feedback. Tri-iodothyronine binds to anterior pituitary nuclear receptors. In the anterior pituitary gland, most of the intracellular T3 is derived from circulating fT4.There for this gland is more sensitive to changes in plasma T4 than to T3 concentrations.

2.3.4 Thyroid function tests

Assessment of thyroid hormone secretion can be made by measuring plasma TSH as well as either fT4 or total T4 [sometimes also free T3 (fT3) or total T3]. Each test has its advantages and disadvantages, although probably most laboratories now offer fT4 and fT3 assays rather than total hormone concentrations. [20]

Plasma thyroid-stimulating hormone

Concentrations of TSH are high in primary hypothyroidism and low in secondary or pituitary hypothyroidism. In hyperthyroidism, high plasma T4 and T3 concentrations suppress TSH release from the pituitary, resulting in very low or undetectable plasma TSH concentrations. Plasma TSH assays are used as first-line assays for thyroid function assessment. New generation assays have high sensitivity and have a detection limit for plasma TSH of less than 0.1 mu/l. (In normal individuals there is a log-linear relationship between plasma fT4 and TSH concentrations; that is tosay, exponential increases in TSH concentration occur with small incremental changes in fT4 concentration.

Plasma T3 and T 4

a) In the plasma 99.95 % of T3 and T4 are transported in association with 2 proteins:

1) Thyroxin binding globulin (TBG): it is the major transporter.

2) Thyroxin binding prealbumin.

b) About .05 % of T3 and T4 are present in a free unbound state. Free T3 and T4 are metabolically active hormones in the plasma.

c) T3 is more active than T4. It may be the only form that binds to receptors of target cells.

d) About 2/3 of the plasma T3 arises by deiodination of T4 in the liver. [20]

2.3.5 Disorders of the thyroid gland

The most common presenting clinical features of thyroid disease are the result of:

- *Hypothyroidism*, due to deficient thyroid hormone secretion.
- *Hyperthyroidism*, due to excessive thyroid hormone secretion.
- *Goiter*, either diffuse or due to one or more nodules within the gland – there may or may not be abnormal thyroid hormone secretion and thus the patient may be euthyroid.

2.3.5.1 Hypothyroidism

Hypothyroidism is caused by suboptimal circulating concentrations of thyroid hormones. It becomes more prevalent with age, affecting about 6 per cent of people over 60 years, and is more common in women.

The condition may develop insidiously and in its early stages may cause only vague symptoms. There is a generalized slowing down of metabolism, with lethargy, bradycardia, depression and weakness.

If the hormone deficiency is caused by a primary disorder of the thyroid gland, the patient may present with weight gain, myopathy, menstrual disturbances, such as menorrhagia, and constipation. The skin may be dry, the hair may fall out and the voice may be hoarse. Subcutaneous tissues are thickened; this pseudo-oedema, with a histological myxoid appearance, accounts for the term myxoedema, which is sometimes used to describe advanced hypothyroidism. In severe cases, coma with profound hypothermia may develop.

The following laboratory changes may be associated with hypothyroidism, particularly if severe:

- Plasma cholesterol concentration. In hypothyroidism the clearance of plasma low-density lipoprotein (LDL) cholesterol is impaired and plasma cholesterol concentrations may be moderately high.

- Plasma creatine kinase activity is often raised in hypothyroidism, due to possible myopathy.

- Hyponatraemia may very rarely present in patients with profound hypothyroidism or myxoedema coma. It is caused by increased antidiuretic hormone release with excessive water retention, occasionally worsened by a constrictive pericardial effusion that some patients develop. [3]

- Hypothyroidism may be associated with hyperprolactinaemia.

- Plasma sex-hormone-binding globulin (SHBG) concentration is reduced in hypothyroidism.

- A macrocytic anaemia may be observed, with raised mean corpuscular volume (MCV).
- In severe hypothyroidism a reduced estimated glomerular filtration rate may occur probably due to impaired renal perfusion. The most common cause of hypothyroidism worldwide is iodine deficiency. In areas of adequate iodine intake, acquired hypothyroidism is mainly due to autoimmune thyroiditis or Hashimoto's thyroiditis, which is more frequently seen in women and the elderly. About 90 per cent of patients have positive thyroid antibodies, for example anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg) or TSH receptorblocking antibodies. There may also be a goiter.

Secondary hypothyroidism is due to low concentrations of TSH from the anterior pituitary or to hypothalamic TRH deficiency; this is much less common than primary hypothyroidism. In long-standing secondary hypothyroidism, the thyroid gland may atrophy irreversibly. The essential biochemical difference between primary and secondary hypothyroidism is in the plasma TSH concentration, which is high in the former and inappropriately low very rarely a 'consumption' hypothyroidism is seen in individuals with extensive haemangioma which contains iodothyronine deiodinase. This selenoenzyme catalyses the conversion of T4 to reverse

Tri-iodothyronine and the conversion of T3 to 3, 3 diiodothyronine, both of which are biologically inactive. [3]

Pathophysiology

Overt primary hypothyroidism (FT4 low; TSH high)

TSH is often increased to more than 20 mu/l, as feedback inhibition of the pituitary is diminished by the low FT4. Measurement of FT3 is unhelpful because normal concentrations are often observed.

The primary causes of hypothyroidism are listed in. Monitoring of thyroid function tests is essential to distinguish the transient from the permanent causes of hypothyroidism, as the former often require no specific treatment. The presence of a goiter. Will distinguish Hashimoto's thyroiditis from atrophic thyroiditis, although the practical utility of separating these groups is limited as both will usually require lifelong replacement of T4. Congenital hypothyroidism will be detected in most countries by neonatal bloodspot screening programs.

Subclinical primary hypothyroidism (FT4 normal; TSH high)

Many cases of subclinical hypothyroidism are transient. It is essential to confirm that abnormalities in TSH are persistent or progressive. Studies suggest that the average patient will not get any clinical benefit from T4 therapy until TSH rises above approximately 10 mu/L. If a profile consistent with subclinical hypothyroidism is found, the tests should be repeated at 3 months to exclude a transient rise in TSH. Measurement of anti thyroid peroxidase antibodies (TPOAbs) can help to determine if an autoimmune process is present and help predict risk of progression to overt hypothyroidism. [1]

Secondary (central) hypothyroidism

Plasma TSH is normal in about half of patients with central (pituitary) hypothyroidism, but FT4 is usually low. Circulating TSH has been shown to have reduced bioactivity in hypopituitarism. It should be stressed that the most common cause of a normal TSH with low FT4 and FT3 is NTI, but it is essential to consider hypopituitarism in all patients with this combination of results. In

patients with secondary hypothyroidism, the objective of replacement therapy is to maintain FT4 in the upper third of the reference range. [1]

Pregnancy and neonatal hypothyroidism in about 0.3 per cent of pregnancies the mother has Hashimoto's disease. Thyroid hormones are essential for fetal development, hence the importance of treating the mother with thyroxine.

Laboratory investigation of suspected hypothyroidism

A careful history (including drugs) should be taken and an examination performed, checking for goitre.

- The plasma TSH and total T4 or fT4 concentrations should be measured.
- Slightly elevated plasma TSH and normal fT4 concentrations suggest compensated hypothyroidism.

2.3.5.2 Hyperthyroidism (thyrotoxicosis)

Hyperthyroidism causes sustained high plasma concentrations of T4 and T3. There is often generalized increase in the metabolic rate, evidenced clinically by, for example, heat intolerance, a fine tremor, tachycardia including atrial fibrillation, weight loss, tiredness, anxiety, sweating and diarrhoea.

The following biochemical features may be associated with hyperthyroidism:

- Hypercalcaemia is occasionally found in patients with severe thyrotoxicosis. There is an increased turnover of bone cells, probably due to a direct action of thyroid hormone. Hypothalamic or pituitary disorder. A TRH test
- Hypocholesterolaemia can occur, due to increased LDL clearance.
- Hypokalaemia may also occur associated with hyperthyrotoxic periodic paralysis.
- Plasma SHBG is increased.
- Plasma creatine kinase may be increased with thyrotoxic myopathy.

Graves' disease this is the most common form of thyrotoxicosis and occurs more often in females than in males. It may be caused by relatively autonomous secretion from a diffuse goitre and is characterized by:

- Exophthalmos, due to lymphocytic infiltration and swelling of retro-orbital tissues of the eyes,

- Sometimes localized thickening of the subcutaneous tissue over the shin (pretibial myxoedema).

Graves' disease is an autoimmune thyroid disease characterized by a variety of circulating antibodies, including anti-TPO, as well as being associated with other autoimmune diseases such as type 1 diabetes mellitus, adrenal insufficiency and pernicious anaemia.

Thyroid antibodies are detectable in some cases, such as thyroid-stimulating immunoglobulin (TSI), which is directed towards epitopes of the TSH receptor and thus acts as a TSH receptor agonist. Nuclear medicine tests may show a high radioactive uptake of iodine by the thyroid gland. [3]

2.3.5.3Thyroiditis

Thyroiditis means inflammation of the thyroid. Thyroiditis encompasses many thyroid disorders, some of which have an autoimmune etiology, including Hashimoto thyroiditis, painless sporadic thyroiditis, and painless postpartum thyroiditis. [27]

Pathophysiology of hyperthyroidism

Plasma T4 or fT4 and T3 and fT3 concentrations are usually increased in hyperthyroidism. Much of the T3 is secreted directly by the thyroid gland, and the increase in plasma T3 concentrations is greater and usually evident earlier, than that of T4. Rarely, only plasma T3 and fT3 concentrations are elevated (T3 toxicosis).

In both situations, TSH secretion is suppressed by negative feedback, and plasma TSH concentrations are either very low or undetectable. [3]

Tests affected by thyroid dysfunction

Several laboratory tests may be affected by changes in thyroid status; it is particularly important to exclude abnormalities in thyroid function in patients with newly diagnosed diabetes, and also those with hypercholesterolaemia. Changes in sex hormone binding globulin (SHBG) concentration can lead to marked changes in the free hormone concentration of testosterone. [1]

Previous study

Study conducted by: Victoria Sy Lim, Victor S. Fang, Adrian I. Katz, and Samuel Refetoff to evaluate thyroid function in patients with end stage kidney disease, and they found: Serum total triiodothyronine concentrations (TT3, ng/100 ml, mean±SD) were 63±17 and 83±22 in the non-HD and HD groups, respectively. Values from normal subjects were 128±25 and from RT patients 134±20. The TT3 was in the hypothyroid range (<78 ng/100 ml; 2 SD below normal mean) in 80% of non-HD and 43% of HD patients. Mean serum total thyroxine concentration (TT4), although within the normal range, was lower than the control value. T4-binding globulin capacity was also slightly lower but the difference was not statistically significant. Among patients whose TT4 was 1 SD below the normal mean, the free T4 index was equally depressed, suggesting that factors other than decreased binding capacity might be responsible for the low TT4. In addition, there was a 37% incidence of goiter. Mean serum thyroid-stimulating hormone (TSH) was not elevated and the TSH response to thyrotropin-releasing hormone (TRH) was distinctly blunted, suggesting the possibility of pituitary dysfunction as well. In vivo 125I-l-T4 and 131I-l-T3 kinetics during 0.2 mg/day of l-T4replacement showed marked reduction in T3 turnover rate in the uremic patients, both before and during HD; the values (μm T3/day, mean±SD) for the different groups were as follows: normal, 33.8±6.1; non-HD, 13.5±2.6; HD, 12.9±3.1; and RT, 30.3±7.1. The low T3 turnover rate was due to impaired extra thyroidal conversion of T4 to T3. The mean percents of metabolized T4 converted to T3 were 37.2±5.8 in normal subjects, 15.7±3.1 in non-HD, 12.8±1.7 in HD, and 34.0±14.7 in RT patients. [28]

Chapter Three

Materials and Methods

3: Material and Methods

3.1: Study design

Descriptive, cross section study, conducted in Shendi town in the period from April to July -2018 that aimed to measure thyroid hormone triiodothyronin (T3) and thyroxine (T4) in renal diseases patients.

3.2: Study area

The study was done in Shendi town which is located in the north of Sudan and north of the capital Khartoum and for about 173km, located in the east side of the river Nile, and covering area about 30km, the population about .most of people are farming. It contain two hospitals and health centers, also there is Shendi University with various faculties like faculty of medicine and health science.

3.3: Study population

Our study conducted on known, diagnosed renal failure patients who attended in Elmek Namir dialysis center

3.4 Sampling

Total 70 samples collected on heparin anticoagulant, 40 samples from renal diseases patients and 30 samples as control from normal people.

3.5: Data collection tools

Information from renal diseases patients was collected in questionnaire.

3.6: Data collection technique

Venous blood collected with anticoagulant (heparin) was taken for measure of thyroid hormone $T_3$and T_4.

3.7: Method used for estimation

Triiodothyronin (T3) and Thyroxin (T4)

Principle

The STAIA-PACK TT3 or T4 is competitive enzyme immunoassay which is performs entirely in the STAIA-PACK TT3 or T4 test cups. T3or T4 which is displaced from its binding proteins by ANS (8-anilin-1-naphthalene suifonic acid) and free T3or free T4 present in the test sample compete with enzyme –

labeled T3orT4 for a limited number of binding sites on a T3or T4 specific antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme – labeled T3 orT4 and are then incubated with a fluorogenic substrate .4-nethylumbelliferyl phosphate (4-MUP). The amount of enzyme – labeled T3or T4 that binds to the beads is inversely proportional to the T3 or T4 concentration in the test sample. A standard curve using a range of known standard concentrations is prepared and unknown T3 or T4 concentrations are calculated using this curve.

Reference Range

T3 = 0.79-1.58ng/ml (1.22-4.43nmol/l)

T4 = 4.9-11micro g/dl (63.2-141.9nmol/l)

3.8: Data analysis

The gathered data was analyzed with Statistical Package for Social Science software program, also t-test was used for calculating degree of variation , *p*.value ,<0.00 is considered significant variation**.**

Chapter Four

Results

4: Results

Table (4.1) Relationship of mean of T3 between test and control groups

Study groups	Frequency	Mean of T3 nmol/l	Mean Difference	P.value
Test	40	1.55	0.23	0.016
Control	30	1.78		

Table (4.2) Relationship of mean of T4 between test and control groups

Study groups	Frequency	Mean of T4 nmol/l	Mean Difference	P.value
Test	40	79.68	22.43	0.010
Control	30	96.11		

Table (4.3) Illustrate the mean of T4, T3 according to gender

Gender	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Male	23	57.5%	77.36	1.52
Female	17	42.5%	82.81	1.59
P.value			.57	.60

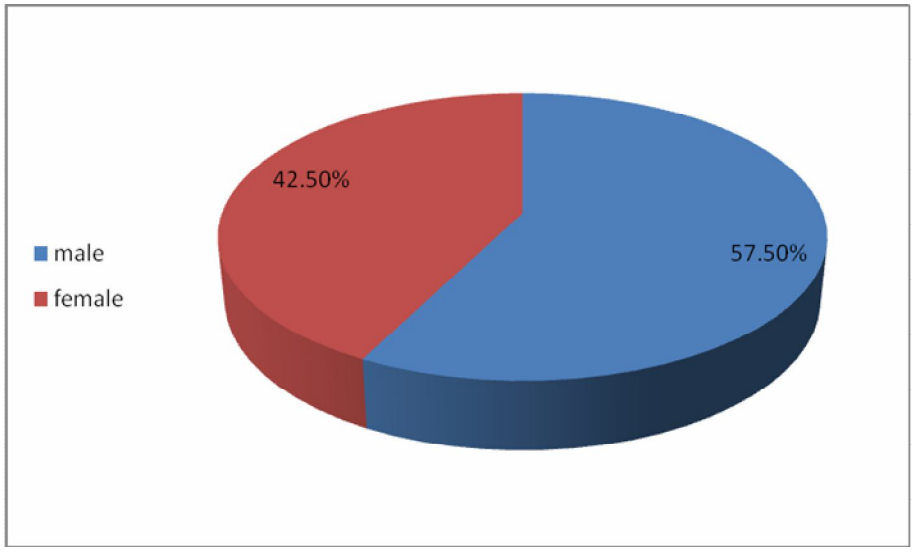

Figure (4-1): Shows the distribution of study group according to gender

Table (4. 4) Illustrate the mean of T4, T3 according to age

Age groups	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
20-40 years	12	30.0%	95.29	1.78
41-60 years	19	47.5%	78.82	1.49
61-80 years	9	22.5%	60.68	1.37
P.value			0.028	0.051

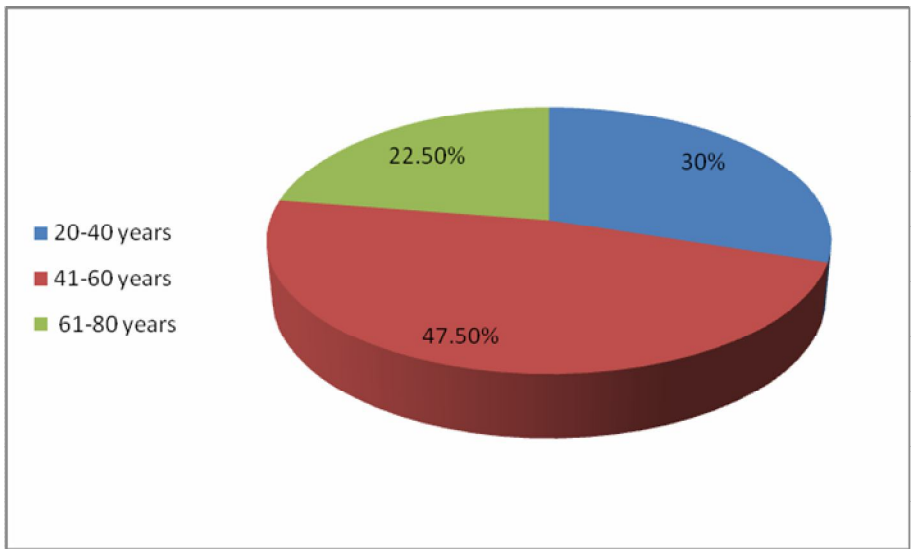

Figure (4-2): Illustrate the distribution of study group according to age

Table (4. 5) Illustrate the mean of T4, T3 according to weight

Weight	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Less than 70kg	23	57.5%	82.75	1.6557
More than 70kg	17	42.5%	75.52	1.4165
P.value			.458	.067

Table (4. 6) Illustrate the mean of T4, T3 according to Type of diet

Type of diet	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Vitamins	14	35.0%	82.48	1.57
Meats	12	30.0%	67.23	1.43
Car & Vit	4	10.0%	74.88	1.48
Meat & Vit	10	25.0%	92.62	1.72
P.value			.251	.422

Table (4.7) Illustrate the mean of T4, T3 according to patient suffering from other diseases

Other Diseases	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
No other disease	13	32.5%	87.31	1.71
Hypertension	18	45.0%	76.23	1.49
D.M	1	2.5%	63.00	1.48
Hyper & D.M	8	20.0%	77.13	1.4
P.value			.712	.418

Table (4. 8) Illustrate the mean of T4, T3 according to duration of renal disease

Duration	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
0-3yrs	25	62.5%	86.43	1.63
4-6yrs	13	32.5%	72.01	1.47
7-9yrs	2	5.0%	45.12	1.20
P.value			.090	.252

Table (4.9) Illustrate the mean of T4, T3 according to duration of dialysis

Duration	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Less than 1yrs	7	17.5%	87.40	1.65
1-3 yrs	25	62.5%	79.48	1.55
More than 3 yrs	8	20.0%	73.52	1.471
P.value			0.682	0.721

Table (4. 10) Illustrate the mean of T4, T3 according to family history of thyroid diseases

Thyroid disease	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Yes	8	20.0%	66.35	1.34
No	32	80.0%	83.01	1.61
P.value			.1630	.0930

Table (4. 11) Illustrate the mean of T4, T3 according to family history of renal diseases

Family history	Frequency	Percentage	Mean of T4 nmol/l	Mean of T3 nmol/l
Yes	9	22.5%	82.14	1.63
No	31	77.5%	78.96	1.53
P.value			.784	.498

Chapter Five

Discussion
Conclusion
Recommendations

5.1 Discussion

This is a descriptive, case control study conducted in Shendi city during the period from March – July 2018, and aimed to measure the thyroid hormone level (T3 and T4) in renal diseases patients

Statistical analysis of gathered data reveals that; mean of thyroid hormone in case group of T3 was (1.55nmol/l) and T4 was (79.68nmol/l) while mean of control group of T3 was (1.78nmol/l) and T4 was (96.11nmol/l) , with p .value of (0.016) and (0.010) respectively, which is less than 0.05 indicating that there were statistically significant variation between case and control group in thyroid hormones level ,i.e.; Low level of thyroid hormones associated with renal diseases patients as shown in table 4.1 and 4.2).

This study degree with the previous study is Victoria Sy Lim, Victor S. Fang, Adrian I. Katz, and Samuel Refetoff (this article has been cited by other articles in PMC).

Statistical significant variation of mean of T3 and T4 between cases among age show in table (4. 4) and figure (4. 2).

Statistical insignificant variation of mean of T3 and T4 between case among gender shown in table 43 and weight shown in table (4.5) and type of diets shown in table (4.6).

Also statistical insignificant variation of mean of T3 and T4 between case among effect of other diseases and duration of renal disease and family history of thyroid disease and renal disease showed in table (4.7), (4.8), (4.9), (4.10), and (4.11) respectively.

5.2 Conclusion

On the basis of the study results we can conclude the following:

- Low thyroid hormones level (T3and T4) in patient with renal diseases.
- lowering in thyroid hormones level (T3and T4) among increase in age.
- There is no effect of other parameter on thyroid hormone level in our study (weight, gender, types of diets, duration of renal diseases and dialysis, family history of renal disease and thyroid diseases).

5.3 Recommendations

By the end of our study; we recommended that:

-Nutrition is rich with iodine (eg fishes) to prevent thyroid disorder.

-Regular evaluation of thyroid hormones level in renal diseases patients.

- Other study must be conducted with large sample size and full thyroid function test (TSH, T4, T3, fT3, fT4).

Chapter Six

References

Appendix

6.1 References

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6.2 Appendix

Shendi University

Faculty of post graduate studies and scientific research

Questionnaire of measure thyroid hormones level in renal diseases patients

1-Gender:

Male ( ) Female ( )

2-Age: ……years.

3-wieght: ……kg

4-Type of diets:

a) Lipids ( ) b) Carbohydrates ( ) c) vitamins ( )

d) Meats ( )

5-Patient suffering from other diseases:

a) Hypertension ( ) b) D.M ( )

c) Hematological diseases ( ) d) other diseases ( )

6-Duration of renal diseases: ……years.

7-Duration of dialysis: …… years.

8-Family history of thyroid disorders:

Yes ( ) No ( )

9-Family history of renal diseases:

Yes ( ) No ( )

Level of T3----------nmol/l

Level of T4----------nmol/l