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فعاليه الجهاز السمبثاوي للُبّ الغده الكظريه بعد التعرض للموجات الصادمه لجهاز تفتيت الحصى الكلويه

رسالة مقدمة الى

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من قبل

رسل عبد الكاظم محمد

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Sympathetic Activity of Adrenal Medullae Following Renal Extra Corporeal Shock Wave Lithotripsy (ESWL)

A Thesis

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الخلاصه

تفتيت الحصى بالموجات الصادمه من خارج الجسم هو الطريقع الاكثر شيوعا لعلاج حصى الكلى وحصى اعلى الحالب ،ويستخدم بالعادة لمعالجة الحصى ذات الحجم الاصغر من ٢ سم ، وسبب انتشار علاج الحصى بالموجات الصادمه ذلك لفعاليته العاليه، نسبة الامان المرتفعه، لايحتاج الى تداخلجراحي " اي يمكن تفتيت الحصى من خارج الجسم "،وكذلك يتم العلاج دون الحاجه الى رقود المريض في المستشفى .

لكن على الرغم من نسبه الامان العاليه،هناك بعض المضاعفات للمرضى التي قد تحدث باستخدام الموجات الصادمه ، هذه المضاعفات قد تكون ب اصابه النسيج الكلوي او انسجه الاعضاء المحيطه بها ،ولكون موقع لب الكظر (الجزء الداخلي من الغده الكظريه المحيطه ب الكليه المتكون من خلايا اليفة الكروم التي تتحفز بواسطه الجهاز العصبي الودي لافراز الكاتيكولامين) ملاصق جدا للكليه، قد يجعلها عرضه للموجات الصادمه المستخدمه لعلاج الحصى .

تهدف هذه الدراسه لمعرفة تاثير الموجات الصادمه الصادمه المستخدمه لعلاج الحصى الكلويه على الجهاز الودي العصبي للب الكظري وذلك بقياس نسبه الكاتيكولامين في الدم قبل جلسه العلاج وبعدها .

اجريت هذا الدراسة في وحده تفتيت الحصى باستخدام الموجات الصادمه،مستشفى الحله التعليمي ،محافظة بابل، من الاول من شهر تشرين الاول لسنه ٢٠٢١ لغاية الاول من شهر نيسان لسنه ٢٠٢٢، الدراسه شملت خمسين مريض ،تم احالتهم من اخصائي الجراحه البوليه لقسم تفتيت الحصى للمره الاولى ،بعد تشخيصهم ب الاصابه بالحصى الكلويه بالاعتماد ع التصوير الشعاعي .

تم اخذ التاريخ المرضي والفحص السريري وسحب عينه من دم المرضى مباشره قبل اجراء جلسه العلاج وفور الانتهاء منها بغضون خمس دقائق،واجراء التحليلات المختبريه لعينات الدم .

اظهرت النتائج لهذه الدراسه ان النسبه الاعلى من المرضى كانوا من الذكور،ومتوسط العمر لديهم (٤٤,٤ ±١٣,٥٦) سنه ،ومتوسط مؤشر كتله الجسم للمرضى كانت (٢٩,٠٥ ± ٤,٤٨)،

٦٦% منهم كانوا لديهم تاريخ مرضي ،٥٥% من المرضى كانو لديهم تاريخ عائلي لحصى الكلى، حصى القطب السفلي من الكليه كان الاكثر شيوعاً في هذه الدراسه حيث شكلت نسبه ٦٠% من الحصى، و ٧٠% منها كانت من النوع المعتم شعاعياً.

اظهرت هذا الدراسه ارتفاع ملحوظ (**p<0.001**) لضغط الدم الانقباضي والانبساطي الشرياني بعد انتهاء جلسه العلاج ،وكذلك ارتفاع ملحوظ (**p<0.001**) في معدل سرعه نبضات القلب . كذلك اظهرت قراءه نسبه السكر في الدم ارتفاع ذات دلاله معنويه في نسبه السكر بالدم (**p<0.001**) بعد الجلسه العلاجيه مباشره .

كذلك اظهرت الدراسه ارتفاع ملحوظ (**p<0.001**) في نسبه الكاتيكولامين (للابنفرين و النورأبنفرين) في مصل الدم بعد جلسه العلاج مباشره ،وكان هذا الارتفاع بصوره اكبر للمرضى الذين تم علاجهم لاصابتهم ب حصى القطب الاعلى للكلى.

وتبين من خلال النتائج هناك ارتفاع ملحوظ في نسبه الدوبامين في مصل المرضى مباشره بعد اجراء الجلسه (**p<0.001**)، لكن نسبه ارتفاع الدوبامين لم تتاثر بموقع الحصى ز

نستنتج من خلال الدراسه ان علاج المرضى ب استخدام الموجات الصادمه له ارتباط ب ارتفاع ضغط الدم الشرياني وتسارع نبضات القلب، كذلك ارتفاع معدل السكر في الدم ،وكذلك ارتفاع ملحوظ في نسبه الكاتيكولامين (ابنفرين ، النور ابنفرين،والدوبامين) بعد الجلسه مباشره .

Summary

Extracorporeal shock wave lithotripsy is the most widely used procedure for treating kidney and upper ureteric stones smaller than 2 cm due to its effectiveness, safety, non-invasive and an outpatient procedure. Despite being safe, ESWL has many complications, some of which may affect renal tissue or extrarenal tissue. Adrenal medullae are one of the extrarenal structures that surround the kidneys, found just above both kidneys and stimulated by sympathetic nervous system resulting in triggering of chromaffin cell to secret catecholamine.

This study aimed to study the effect of Extracorporeal shock wave lithotripsy on the sympathetic activity of adrenal medullae in patients with renal stone by measuring the catecholamine level before and after ESWL session.

This cross-section study was performed at the extra-corporeal shock wave lithotripsy unit, Al-Hilla Teaching Hospital, Al-Hilla province/Iraq, from 1st of October/ 2021 to 30th of April /2022. Fifty patients were included in this study; they were referred by a urologist to an ESWL unit for the first time after being diagnosed with kidney stones according to imaging modalities.

Before and immediately after an ESWL session, patients underwent a history, physical examination, and laboratory tests to measure their levels of catecholamines.

The result of this study showed that most patients with renal stone were male, mean age of patients was (44.40 ± 13.56) years, mean body mass index (29.05 ± 4.48) kg/^{m2}, 66% of patients were positive past medical history and 55 % had family history of renal stone.

The lower pole renal stones were the most prevalent, accounting for 60% of all renal stones, and 70% of them were opaque.

There was significant change of systolic and diastolic blood pressure after ESWL session of p value (<0.001), significant elevation of pulse rate following session with p value (p<0.001), and there are significant differences of blood glucose level post session (p <0.001).

This study revealed that there is significant increase of serum epinephrine and norepinephrine value (p <0.001) following ESWL, and there is significant increase in epinephrine and norepinephrine levels in patients treated with upper pole renal stone with p value (0.008 ,0.037) respectively.

Regarding the measurement of dopamine levels showed that there was a significant increase in dopamine levels after the session (p< 0.001), although dopamine levels were unaffected by altering the lithotripter's parameter (energy, frequency, and the number of shock waves). The correlation between the stone's location and dopamine levels was not significant.

The study concluded that there is significant association between undergoing extracorporeal shock wave lithotripsy session and sympathetic activity of adrenal medullae, as patients receiving shock waves have increase in their blood pressure, heart rates, and blood glucose levels. Catecholamine levels are significantly rising post session, the rising of epinephrine and norepinephrine were more considerable in patients treated with upper pole renal stone.

1 Introduction

1.1 Background

Extra-corporeal shock waves lithotripsy (ESWL) is the only fully, non-invasive, outpatient method for the treatment of urinary tract stones. ESWL's effectiveness is predicated on its capacity to pulverize calculi in vivo into smaller segment, which the kidney then expels spontaneously (Demir and Barlas, 2022).

Over 30s years, the lithotripters which provide the energy required for this treatment, have gone through a number of advancements and adjustments, the electrohydraulic (HM-1) lithotripter was first described in 1980, and shortly followed by the electrohydraulic Dornier HM-3 lithotripter Currently, advances in lithotripter models allow for shock wave generation from electromagnetic, piezoelectric, and electroconductive technologies. Second- and third-generation lithotripters have also utilized more narrow focal zones and higher peak pressures when compared to the wider focal zones and lower pressures utilized by firstgeneration lithotripters (Manzoor and Saikali, 2021).

The selection between shockwave lithotripsy (SWL) and alternative treatment modalities is based on various of factors, including the size of the stone, burden, and composition. ESWL is regarded a reasonable first-line treatment for non-staghorn renal and ureteral calculi that are smaller than 2 cm in size (Türk *et al*., 2016).

Despite the fact that it is noninvasive and safe modality, it has certain adverse implications, these adverse effects can be attributed to obstructive complications associated with stone passage, direct tissue damage, or both (Pearle, 2012). Studies have shown that ESWL has a direct effect on extra-renal tissue. An earlier study (on rats) revealed that the tissues surrounding the kidney, including the adrenal gland, showed a histological changes after being exposed to shock waves lithotripsy (Gecit *et al*., 2012).

Adrenal gland is a pair of small, triangular-shaped glands located on top of both kidneys, made up of the cortex and medulla. The adrenal cortex is the largest part, has 3 distinct functional and histological zones, produces steroid hormones including glucocorticoids, mineralocorticoids, and adrenal androgens (Dutt and Ishwarlal, 2019).

The adrenal medulla is the innermost part of the gland, comprised almost entirely of catecholamines secreting cells called chromaffin cells. It is innervated by typical preganglionic sympathetic neurons, which stimulates catecholamine secretion, which act on adrenergic receptors located in multisystem smooth and adipose tissue (Maestroni, 2019).

Catecholamines regulate blood pressure by contracting smooth muscle in the vasculature. Muscles activities include increased heart contractility, pupillary dilator muscle contraction, piloerection, and smooth muscle relaxation in the gastrointestinal tract, urinary tract, and bronchioles. In addition, stimulate glycogenolysis in the liver, increased glucagon secretion, and decreased insulin secretion from the pancreas, as well as lipolysis in adipose tissue, to boost blood glucose levels (Paravati and Warrington, 2019).

1.2 Aim of study

The objective of this study is to illustrate the effect of renal extracorporeal shock waves lithotripsy on sympathetic activity of adrenal medullae.

2 Review of literature

2.1 Adrenal glands

Each of the two adrenal glands, which weighs around 4 grams, is located at the superior pole of both kidneys. The adrenal medulla and cortex, which make up each gland, are its two main components (Burford *et al*.,2017).

2.1.1 Adrenal cortex: -

The outer and the largest part of an adrenal gland, its divided into three separate zones (Gallo *et al*.,2014): -

1-Zona glomerulosa: - a thin layer of cells that lies just underneath the capsule, constitutes about 15 percent of the adrenal cortex. The main site of aldosterone production, synthesis and secretion of aldosterone is under control of renin-angiotensin-aldosterone system.

2- Zona fasciculata, the middle and widest zone, constitutes about 75 percent of the adrenal cortex and secretes the glucocorticoids cortisol and corticosterone, as well as small amounts of adrenal androgens and estrogens. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via adrenocorticotropic hormone (ACTH).

3- Zona reticularis: -The inner most cortical layer of adrenal cortex, which produces adrenal androgens, mainly dehydroepiandrosterone (DHEA) and androstenedione, as well as small amounts of estrogens and some glucocorticoids. ACTH also regulates secretion of these cells, although other factors such as cortical androgen-stimulating hormone, released from the pituitary, may also be involved.

2.1.2 Adrenal medulla

It’s the innermost part of adrenal gland and represent about 20% of adrenal gland, being surrounded by adrenal cortex, consisting of chromaffin cells that responsible for secretion of catecholamine, including epinephrine (adrenaline), norepinephrine (noradrenaline), and small amount of dopamine in response to stimulation by sympathetic preganglionic neuron (Yasir *et al*., 2021).

2.1.2.1 Physiologic anatomy of adrenal medulla: -

Stimulation of the sympathetic nerves to the adrenal medullae causes large amounts of epinephrine and Norepinephrine to be released into the bloodstream, and the blood then transports these two hormones to all of the body's tissues. In general, epinephrine makes up around 80% of the secretion and norepinephrine makes up 20%, though the relative proportions can vary greatly depending on the physiological situation (Hall, 2016)

The effects of circulating epinephrine and norepinephrine on the various organs are almost identical to those brought on by direct sympathetic stimulation, with the exception that they last 5 to 10 times as long because both of these hormones are slowly removed from the blood over the course of 2 to 4 minutes (Paravati and Warrington, 2019).

The “fight or flight” response of the sympathetic nervous system is a direct result of the multisystem action of catecholamines. Secretion from the adrenal medulla preceding the activation of the sympathetic nervous system functions to regulate blood pressure by contracting the smooth muscle in the vasculature (via alpha-1 receptors).

The adrenergic receptors linked to blood vessels have an especially high affinity for norepinephrine relative to the other amines. Further musculoskeletal actions of catecholamines include enhanced contractility of cardiac muscle (via beta-1 receptors), contraction of the pupillary dilator (via alpha-1 receptors), piloerection (via alpha-1 receptors), and relaxation of smooth muscle in the gastrointestinal tract, urinary tract, and bronchioles (via beta-2 receptors). Both epinephrine and norepinephrine modulate metabolism to increase blood glucose levels by stimulating glycogenolysis in the liver (via beta-2 receptors), increased glucagon secretion (via beta-2 receptors), and decreased insulin secretion (via alpha-2 receptors) from the pancreas, and lipolysis in adipose tissue (via beta-3 receptors).

Epinephrine also inhibits the release of mediators from mast cells and basophils in type I hypersensitivity reactions (ScottCoombes, 2015).

Nearly identical actions are produced by epinephrine and norepinephrine, although they differ in the following respects:
First, epinephrine has a stronger impact on stimulating the beta receptors than norepinephrine, which in turn has a stronger effect on exciting the heart (Lim, 2019).

Second, in contrast to the much stronger constriction generated by norepinephrine, epinephrine just slightly constricts the blood vessels in the muscles. Because the muscle vessels make up a major a significant portion of the vessels of the body, this difference is of particularly important because norepinephrine greatly increases the total peripheral resistance and elevates arterial pressure, whereas Epinephrine raises the arterial pressure to a lesser extent but rises the cardiac output more (Lim, 2019 ;Yasir *et al* ., 2022).

A third difference between the actions of epinephrine and norepinephrine relates to their effects on tissue metabolism, as the metabolic impact of epinephrine is 5 to 10 times greater than that of norepinephrine. In addition, the epinephrine generated by the adrenal medullae can raise the metabolic rate of the entire body to levels up to 100% higher than average, enhancing the body's activity and excitability (Boron and Boulpaep, 2012).

2.1.3 Catecholamine: -

The chemical neurotransmitters and hormones known as catecholamines, which include dopamine, norepinephrine, and epinephrine, have important roles in the control of physiological processes as well as the development of neurological, psychiatric, endocrine, and cardiovascular diseases (Chakravarthy *et al*., 2018).

2.1.3.1 Catecholamine biosynthesis: -

Tyrosine serves as the main raw material for the synthesis of catecholamines. Tyrosine is either produced in the liver from dietary phenylalanine or is obtained directly from food sources. Tyrosine is metabolized into dopamine by the enzyme’s tyrosine hydroxylase and aromatic-L-amino acid decarboxylase through a series of enzymatic changes. Dopamine can be transformed to norepinephrine by dopamine b-hydroxylase. Phenyl ethanolamine N-methyltransferase (PNMT), an enzyme found in chromaffin tissue of adrenal medulla, is necessary for the conversion of norepinephrine to epinephrine. Cortisol from the adrenal cortex increases PNMT which, also promotes, increases epinephrine production (Boron and Boulpaep, 2017).

2.1.3.2 Catecholamine metabolism: -

The neuronal absorption of catecholamines through certain transporters, preceded by inside active transport into storage pools, prevents the majority of catecholamines released from sympathetic nerve storage vesicles from reaching the bloodstream.

These pools have a steady dynamic equilibrium that is regulated by vesicular monoamine transporters (VMAT) leading to a leakage into the cytoplasm of catecholamines that are also available for oxidative deamination by monoamine oxidase (MAO) into 3,4dihydroxyphenylglycol (DHPG) (Baranowski *et al*., 2018).

Catecholamines may additionally enter non-neuronal tissues to be methoxylated into metanephrines and normetanephrine (Epinephrine to metanephrines, Norepinephrine to normetanephrine) by catechol-Omethyl transferase (COMT). The adrenal medulla chromaffin cells, in contrast to sympathetic neurons, express COMT and may also create metanephrines. However, extra neuronal O-methylation of Nepinephrine and Epinephrine to metanephrine represents insignificant metabolic pathways in comparison to intraneuronal deamination. Oxidation of MN and NMN by MAO or methoxylation of DHPG by COMT leads to the formation of methoxyhydroxyphenylglycol (MHPG) that is further metabolized in the liver into vanillylmandelic acid (VMA). These mechanisms help to somewhat explain the plasma catecholamines' short half-life (Leviel, 2011).

Before entering the systemic circulation, the dietary source of catecholamines is sulfoconjugated in the gastrointestinal tract by the specific sulfotransferase isoenzyme SULT1A3. As a result, meals have no effect on the free catecholamine concentrations that are measured in plasma and urine (Eisenhofer *et al*., 2004).

Unconjugated dopamine in urine is tenfold more prevalentt than Norepinephrine since it is produced by renal extraction and decarboxylation of circulating 3,4-dihydroxyphenylalanine (L-DOPA) obtained by food and may potentially be a misleading parameter for pheochromocytoma detection.

The metabolism of dopamine shows similar extra neuronal metabolism by COMT and MAO leading to the formation of 3methoxytyramine (MT) and 3,4-dihydroxyphenylacetic acid (DOPAC). DOPAC undergoes O-methylation to produce homovanillic acid (HVA) as an end-product Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by exocytosis. Once in circulation, catecholamines can exist in the plasma either free form or conjugated with other molecules. After the gland is activated, norepinephrine and epinephrine are produced within seconds and may enter into full function within a further few seconds to minutes (Leenen *et al*., 2007).

An earlier study (on rats) revealed that tissue surrounding the kidney, adrenal gland, showed histological changes after being exposed to shock waves lithotripsy in patients with renal stone treated by it (Gecit *et al*., 2012).

2.2 Urolithiasis: -

Urolithiasis is a serious health problem that has an influence on all societies. Its frequency and incidence have been rising in numerous regions of the world. About 12% of the world's population is affected by this growing urological illness. It has been linked to a higher risk of renal failure in its late phases. Kidney stone etiology is multifactorial, recurrent kidney stone prevention is still a significant health issue for people (Moe, 2006).

2.2.1 Epidemiology and risk factors: -

The prevalence of the disease rises from east to west, affecting one to five percent of Asian, five to ten percent of European, and thirteen percent of North American civilizations, respectively (Ahmad *et al*., 2018). A ratio of 2.4:1 showed that urinary calculi were more prevalent in male than in female (Khan *et al*., 2017), because men consume more protein in their diets than women do, which enhances their risk of developing stones (as higher protein intake increases urinary excretion of calcium and uric acid, and reduce citrate and urine PH, thus potentially favoring formation of calcium and uric acid stones). Contrarily, estrogen in women have a main role in decreased risk of renal stone formation by, reduces surface expression of two calcium oxalate crystal receptors, reduces crystal binding capability and reduces intracellular ATP in renal tubular cells, also estrogen increases the amount of citric acid that they produce, decreasing the possibility that urinary tract calculi would form (Alkhunaizi, 2016).

Additionally, climatic change has an impact on the prevalence of renal stones; they are more likely to develop in people who have lived in moderate climates as opposed to cold climates, and they are more likely to do so during the hot season of the year as compared to the cold, the incidence of crystallization and the formation of stones is enhanced by decreased fluid intake, increased sweating, and increased urine concentration. Recent large-scale epidemiologic studies have revealed a rise in the occurrence of kidney stones in people with lifestyle-related illnesses such hypertension (HTN), diabetes mellitus (DM), obesity, and dyslipidemia (DL). Metabolic syndrome is the collective term for these interconnected risk factors (Chen *et al*., 2019).

In addition, there are other risk factors for the development of stones, including lifestyle habits and dietary/nutritional factors, genetic predisposition/inherited disorders, Anatomical abnormalities, Metabolic conditions: including hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and a history of gout, hypercalcemic disorders, race, age, socioeconomic status, occupation Lithogenic drugs: such as indinavir (Crixivan),sulfonamides (Alelign and Petros, 2018).

2.2.2 Urinary system and stone formation: -

The glomerulus produces the urine filtrate, which then travels into the tubules where reabsorption or secretions change its volume and composition. The proximal tubules are where most solute reabsorption takes place, while the distal tubules and collecting ducts are where small modifications to urine composition are made.

The loop of Henle is used to concentrate urine, The essential nutrients such as amino acids, proteins, bicarbonate, calcium, phosphate, and potassium are also reabsorbed and returned to the blood stream in the proximal tubules along with glucose, salt, chloride, and water. The distal tubule controls the blood's salt and acid-base balance (Barbas *et al*., 2002), the stones' location might change, as shown in figure (2-1)

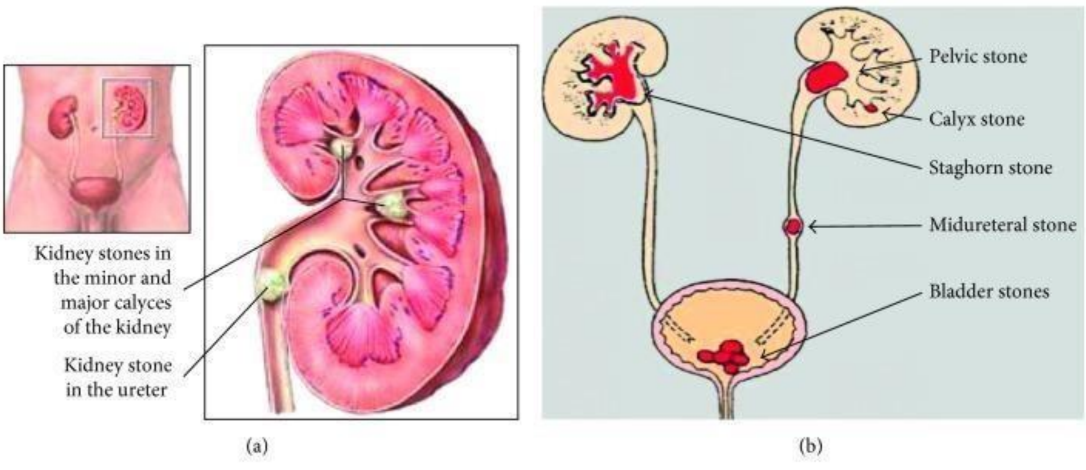

Figure (2-1): -kidney stone locations in the urinary system, a: oclations of stones inside kidney, b: location of stones in urinary system (Evan, 2010).

2.2.3 Renal stones formation: -

A biological process called renal stone formation includes supersaturation of urine and physicochemical changes. The uneven proportion of inhibitors and promoters are responsible to the complex process of stone formation in kidneys or urolithiasis. Supersaturation of the urine with calcium and oxalate salts followed by crystalline particle formation is the major reason behind kidney stone formation with supersaturation being the driving force (Khan and Kok, 2004).

The mechanism involved in the process of stone formation, include nucleation of crystals fractions, growth or gathering of these crystals to a size so that they can interact with some intra-renal structure(s), confinement of these crystals inside the kidney or renal collecting system succeded by further aggregation and/ or secondary nucleation ultimately forming the clinical stone .Calcium oxalate (CaOx) forms the major proportion of the kidney stones that is around 80% , while calcium phosphate (CaP) forms a small percentage (15%) of these stones .

The crystals formed either in renal tubular fluid or in the renal interstitial fluid that is supersaturated with respect to these constituents, which in turn might be a consequence of reduced urine volume, an alteration in urine pH, mechanisms causing increased secretion of stone forming constituents such as hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria or a combination of these factors (Aggarwal *et al*., 2013).

The urine and presumably, the tubular fluid of stone formers are often more highly supersaturated than that of normal healthy adults, which favors nucleation and growth of crystals. Long-term accretion of additional elements, crystalline as well as organic matrix produces the clinical stone. As already explained extreme excretion of calcium or oxalate either alone or in combination as well as low volume of urine leads to an enhanced calcium oxalate supersaturation. The reciprocal actions between genetic susceptibility and environmental factors in different proportions promote both hypercalciuria and hyperoxaluria (Cunningham *et al*., 2016).

A few genetic disorder which a rare autosomal recessive disorder, dietary routine including greater intake of oxalate and low calcium intake, potential abnormalities of anion transporters found in both gut and kidney, enhanced absorption of oxalate in the intestines other than mal absorptive diseases (enteric hyperoxaluria), changes in the normal flora of the gut thereby decreasing degradation of oxalate in the colon may cause one form of hyperoxaluria called primary hyperoxaluria types 1 and 2. Some rare genetic disorders such as adenine phosphoribosyltransferase (APRT) deficiency, cystinuria, and Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) and primary hyperoxaluria may lead to severe or chronic kidney stone diseases in children .

The abovementioned processes in humans are influenced by several factors known as promoters and inhibitors. Among the promoters of calcium oxalate stones are high oxalate, sodium, calcium, urate, low urine pH and low urine volume while the inhibitors include organic substances such as nephrocalcin and urinary prothrombin fragment 1, osteopontin and various inorganic substances such as citrate, magnesium (Basavaraj *et al.*, 2007).

2.2.4 Types of renal stones: -

Kidney stones are often divided into five kinds based on variations in mineral composition and pathophysiology, as follow:

1-Calcium-Based Calculi (calcium oxalate and calcium phosphate)

About 80% of all urinary calculi are calcium stones, which predominate among renal stones. The percent of calcium stones may be composed up of primarily calcium oxalate (CaOx) (50%) or calcium phosphate (CaP, also known as apatite) (5%), or a mixture of both (45%) (Tandon *et al*., 2010).

Calcium stones are composed mainly of brushite (calcium hydrogen phosphate) or hydroxyapatite. Multiple disorders, including hypercalciuria (resorptive, renal leak, absorptive, and metabolic disorders), hyperuricosuria, hyperoxaluria, hypocitraturia, hypomagnesuria, and hypercystinuria, lead to the development of CaOx stones. CaOx stones are typically promoted by urinary pH levels of 5.0 to 6.5, whereas calcium phosphate stones develop when pH is higher than 7.5. Compared to other kidney stone types, calcium stones tend to recur more frequently (Assimos, 2017).

2-Struvite or Magnesium Ammonium Phospate Calculi: -

Struvite stones, also known as infection stones and triple phosphate stones, occurring in 10-15% of patients, in individuals with chronic urinary tract infections that produce urease, the commonest is Proteus mirabilis, whereas less common pathogens include Klebsiella pneumonia, Pseudomonas aeruginosa, and Enterobacter (Meyers and Naicker, 2021). Urease is an enzyme that hydrolyzes urea into ammonia and carbon dioxide, which elevates the pH of the urine to a higher level (usually > 7).

Since phosphate is less soluble at an alkaline pH than it is at an acidic pH, it precipitates on the insoluble ammonium products, resulting in the development of huge staghorn stones. This form of stone develops more frequently in women than in men. Escherichia coli is not connected to struvite stones and is not able to breakdown urea (Saleh *et al*, 2022).

3-uric acid calculi or urate: -

Uric acid calculi account for 5-10% of all urinary calculi. Hyperuricosuria and urine acidity exacerbate uric acid calculus formation .the most Common cause of uric acid nephrolithiasis is idiopathic, other causes include diet, gout and chronic diarrhea, Compared to the general population, patients with a high body mass index or diabetes have more acidic urine and a considerably higher propensity to develop uric acid calculi, and men are more prone than women to develop uric acid stones (Ekeruo *et al*., 2004)

4-Cystine Calculi: -

Cystine calculi account for 1-3% of all urinary calculi and are primarily a consequence of cystinuria, a metabolic disorder resulting from genetic defects (autosomal recessive disorder caused by a defect in the rBAT gene on chromosome (2) of renal transport resulting in impaired renal tubular absorption of cystine or leaking cystine into urine, It does not dissolve in urine and leads to cystine stone formation (Kim *et al*., 2007).

5-Medication-Induced Calculi: -

This accounts for about 1% of all stone types, Medication-induced calculi may be caused by prolonged or excessive use of some medications. Indinavir sulphate and similar protease inhibitors used in HIV treatment are particularly well-known causes of urinary calculi (Jao and Wyatt,2010). Common herbal supplements that may induce renal calculi include ephedrine, a stimulant and weight loss product, as well as guaifenesin, an expectorant (Bennett et *al*., 2004).

2.2.5 Diagnostic evaluation: -

Evaluation includes a detailed medical history, physical examination, appropriate imaging, and basic evaluation. Regardless of the type of stone, patients present with a similar array of symptoms, ranging from asymptomatic to critically ill. The presentation includes sudden to gradual onset, unilateral colicky abdominal/flank pain that often waxes/wanes, hematuria (90% microscopic on UA), nausea, vomiting, and fever.

Depending on the location of the pain within the urinary tract, pain can range from flank pain when near the ureteropelvic junction to groin/scrotal/labial pain if the stone is at the ureterovesical junction.

In severe cases, stones can cause urinary obstruction and/or can become a source of sepsis. In these patients, symptoms are more severe and include mild confusion to obtundation secondary to severe metabolic abnormalities. In patients that do present with severe infection or sepsis, hemodynamic instability is often present (Wimpissinger *et al*., 2007).

2.2.5.1 Imaging modalities: -

Urolithiasis may be assessed with ultrasound, x-rays computed tomography (CT), or magnetic resonance imaging (MRI).

1- Ultrasound (US):

The primary diagnostic imaging method that should be performed is ultrasound. Sensitivity and specificity for all stones in the US are 19–93% and 84–100%, respectively (Sheno *et al*., 2011)

2-Plain x-ray: -

The most frequently used imaging method is a plain x-ray of the kidney, ureter, and bladder area (KUB). It helps in locating radiopaque calculi of a moderate size and is really simple to perform. For stone identification, KUB radiography has a sensitivity and specificity of 44–77% and 80–87%, respectively (Turney and Keoghane, 2013). The stone's value is obviously low if it exhibits radiolucence. It is also challenging to locate very small stones and distinguish them from other shadows that resemble them, including calcified mesenteric nodes (Pandey, 2017).

The follow-up of patients during or after treatment for stones, particularly after ESWL, is one of the principal purposes of KUB. While the majority of calcium_containing stones(radiopaque) are visible on x-ray, certain stone compositions (eg, cysteine and uric acid stones) are radiolucent and not identifiable on x-rays (Moe, 2006).

Additionally, overlying bowel gas, patient body habitus, and extrarenal calcifications can further limit the diagnostic ability of x-rays. As a result, the sensitivity and specificity have been reported as low as 59% and 71% respectively (Bultitude *et al*., 2016).

3-Computed tomography: -

Non-contrast CT is the most common imaging technique for dignosis individuals with acute urolithiasis. Additionally, CT can be used to identify the type of stone and predict how tough lithotripsy will be
(Elkoushy and Andonian, 2017)

Stone density (measured in Hounsfield units, or HU), skin-to-stone distance, and extracorporeal shockwave lithotripsy (SWL) outcome can all be determined with non-contrast CT, but this information regarding renal function and urine collecting system anatomy is missed, in comparison to other imaging modalities, there is higher risk of radiation exposure (Azal *et al* ., 2020) .In patients with body mass index (BMI) <30 kg / m2, , low-dose CT has sensitivity of 86% for detecting ureteric stones <3 mm ,and 100% for calculi >3mm.A metaanalysis of low-dose CT accuracy revealed pooled sensitivity of 97% and specificity of 95% in patients with urolithiasis (Mahajan, 2019).

4-Magnetic resonance imaging (MRI).

Magnetic resonance imaging (MRI) is of limited value in the investigation of renal calculi as compared to CT. The short imaging time and lack of ionizing radiation risk are two benefits of MRI. Additionally, since the collecting system may be seen by stretching it with intravenous frusemide, there is no requirement for intravenous contrast agents (Leyendecker and Clingan, 2009).

The sensitivity and specificity are 97% ,100% respectively for MRI urogram for stones in the urinary tract including those in the ureter.

Gadolinium produces better sensitivity in establishing the cause of obstruction. If other features, such as peri-renal signal intensity, are also included, the sensitivity increases further. It is important to remember that on MRI, stones are seen as a signal void and cannot be differentiated from a tumor or a blood clot. MRI may miss small calyceal stones. In general CT is superior to MRI in the investigation of renal and ureteric stones. One situation where MRI is invaluable is in pregnancy when it is advisable to avoid exposure to radiation (Sudah *et al*., 2001).

2.2.6 Treatment of renal stones

The treatment of urolithiasis is based upon the patient's acute presentation and includes both conservative medical therapies and surgical interventions. Often when patients present, pain control is an important intervention. Medical expulsive therapy, or MET, includes alpha-blockers, such as doxazosin and tamsulosin, which is a useful adjunct to facilitate passage of larger (5-10 mm) stones but has not shown to be beneficial in the passage of smaller ones. Approximately 86% of stones will pass spontaneously within 30-40 days (Assimos, 2018)**.**

Further interventions should be discussed with urology emergently, and an appropriate plan of care made according to the patient's risk factors, medical history, acute presentation, and urologist's comfort and preference. There are various methods of acute urologic interventions, including flexible ureteroscopy (URS), extracorporeal shockwave lithotripsy (ESWL), and percutaneous nephrolithotomy (PCNL) (Desai *et al*., 2017)**.**

Flexible URS is the most common method used and involves an endoscopic approach passed through the lower urinary tract system into the ureters and calyces. This technique allows for the visualization of the urinary tract and the retrieval of an obstructing stone. Flexible ureteroscopy is a good option for lower pole stones between 1.5 and 2 cm in size (Türk *et al*., 2019).

PCNL is often reserved for patients that fail or have contraindications to URS or ESWL. This method is preferred for stones greater than 20 mm in size, staghorn calculi, and stones in patients with a history of chronic kidney disease. Large stones located in the kidney and proximal ureter are often treated using this technique.

Acute renal obstruction with signs of urinary tract infection is a urologic emergency, this will require emergent decompression to prevent permanent renal damage and worsening of infection. The two options currently present for this are indwelling ureteral catheter and placement of a nephrostomy tube (chande M and Gadhavi J M, 2020).

2.3 Extracorporeal shock wave lithotripsy (ESWL)

2.3.1 History and development: -

Extracorporeal shock wave lithotripsy (ESWL), which was first used primarily for medical purposes in west Germany in the 1980s, In 1984, Chaussy and colleagues first published their experience using extracorporeal shock wave lithotripsy (ESWL) in 852 patients (Chaussy *et al*., 1984) and had a dramatic impact on the treatment of urinary stones, quickly gained acceptance across the world owing to its simplicity, noninvasiveness, high efficacy in treating kidney and ureteral stones, and availability of lithotripters (Egilmez *et al*., 2007). Currently, it is estimated that this technique may manage 90% of upper urinary tract stones with a success rate of 68%-86% (Landau et al.,2009).

An electrohydraulic (EH) lithotripter served as the basis for the first ESWL machine. As technology advanced, new devices like piezoelectric and electromagnetic (EM) lithotripters were developed (Landau *et al*., 2009; Alanee *et al*, 2010).

2.3.2 Indication of ESWL: -

The decision to use shockwave lithotripsy (SWL) vs alternative treatment techniques is influenced by a number of variables, such as stone size, stone location, stone composition, etc. The desires and expectations of the patient can also influence the treatment technique choice (Türk *et al*., 2016).

Extracorporeal shock wave lithotripsy indicated as the first line of treatment for patients with renal stones smaller than 2 cm (Assimos *et al*., 2016). About stone location, the major impact of ESWL is on the stones located in middle calyx, upper calyx, renal pelvis and upper ureter respectively. Stones of Distal ureter and bladder are less affected by

ESWL (Ghalayini *et al*., 2008). Among stones of different types, uric acid and struvite are the most sensitive stones against ESWL while the fragmentation rate of cystine and calcium oxalate monohydrate stones is low (Slavkovic *et al*., 2006).

2.3.3 Types of lithotripters: -

A variety of lithotripters are used in clinical settings, with their main differences between them in the way that they generate shock waves (Auersperg and Trieb, 2020).

1- Electrohydraulic lithotripters: -

Electrohydraulic (spark-gap) lithotripters rely on an underwater discharging of a high-voltage spark, which quickly vaporizes the surrounding water, generating spherically expanded shock, positioning the electrode inside an ellipsoid reflector, allows the shock waves to be directed at the second focal point of the ellipse. Example: Dornier HM3

2- Piezoelectric lithotripters: -

Piezoelectric lithotripters produce shock waves with the employ a spherical dish filled with an array of tiny ceramic elements. In response to a high voltage pulse, these elements rapidly expand, generating shock waves. The spherical shape of the dish allows the shock waves to converge at the center of the radius of curvature where the stone is positioned. Example: PiezoLith of Wolff.

3- Electromagnetic lithotripters: -

Electromagnetic lithotripters composed of an electromagnetic coil (flat or cylindrical coil) and a closely approximated metallic plate (or membrane) inside a water-filled shock tube. When an electrical impulse is applied to the coil, the thin membrane reacts with a repulsive force, thereby producing shock waves that are focused at the focal point by means of an acoustic lens. Examples: - modulith SLX-F2 lithotripter

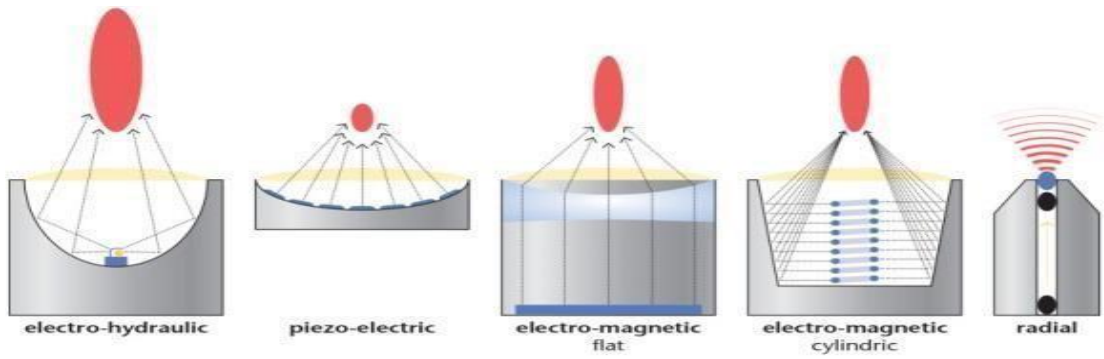

Figure (2-2): - Types of lithotripters

2.3.4 Mechanism of stone fragmentation in the ESWL

Initial fragmentation, similar to the fracture of any brittle object, represents a process whereby cracks form as a result of stresses generated by applied shock waves. Cracks begin at sites where shock wave–induced stress exceeds a critical value. Further disintegration occurs as a result of growth and coalescence of these cracks under repetitive loading and unloading (Lokhandwalla and Sturtevant, 2000). Besides established mechanisms describing initial fragmentation like tear and shear forces, spallation, cavitation, and quasi-static squeezing, further insight was gained by the studies of ((Eisenmenger W *et al*.,2001; Sapozhnikov *et al*., 2007), which introduced the theory of dynamic squeezing as shown in table (2.1).

Table (2.1): - the mechanisms of stone fragmentation by ESWL

Hypothesis	Mechanism	Prerequisites	Type of action	comments
1.cavitation	Negative pressure waves induce a collapsing cavitation bubble at the stone surface.	Low viscosity of surrounding medium.	Microexplosive erosion at the proximal and distal ends of the stone.	More impo-rtant during stone comminution Useful for improving the efficiency of shock waves (ie, EHL)
2.tear and shear force	Pressure gradients resulting from impedance changes at the stone front and distal surface with pressure inversion	Shock wave smaller in space extension than the stone.	Hammer-like action resulting in a crater-like fragmentation at both ends of the stone	Only relevant for small focus zones.
3.spallation	Maximum stress is present at the stone's distal end, where a tensile wave is reflected.	Shock wave smaller in space extension than the stone.	Breaking the stone from the inside like freezing water in brittle material.	Only relevant for small focus zones No explanation for stone breakage
				at the front side.

4.dynamic squeezing	Shear waves initiated at the corner of the stone are reinforced by squeezing waves along the calculus.	Parallel travelling of longitudinal waves Shock wave velocity is lower in the water than in the stone.	Nutcrackerlike action in combination with spalling	Best theory to explain results of the numerical model.
5.Quasi-static squeezing	Pressure gradient between circumferential and longitudinal waves results in squeezing of the stone	Shock wave is broader than the stone Shock wave velocity is lower in the water than in the stone	Nutcrackerlike action requiring large focal diameters	Only relevant for large focal zones

2.3.5 Optimizing Success with ESWL: -

Extracorporeal shock waves lithotripsy is based on predicting stone-free rates. These variables include clinical parameters like patients factors as well as stone factors, like (size, location, diameter, Hounsfield units (HU) and composition) and lithotripter parameter (Park *et al*., 2016).

1-Patients factors: -

Skin-to-stone distance (SSD), a surrogate for BMI, has been shown to affect the stone-free status following SWL. SSD of less than 10 to 11 cm is an independent predictor of a higher successful rate after SWL (Patel *et al*., 2009). Similarly, a higher body mass index (BMI, more than 30 kg/m2) is associated with decreased success, as Obesity provides challenges with on table positioning and radiographic quality (Rassweiler *et al.*, 2011).

Using facilitating fragment passage that promote expulsion of renal and ureteral stone fragments such (α-blocker therapy, and physiotherapy like percussion, diuresis, and inversion (PDI) may assist clearance of stone fragments remaining in the lower pole after SWL (Chiong *et al.*, 2005).

2- Stone factors: -

A. Size: - it is well documented that, as stone size increases, SWL success rates decrease. Investigators have demonstrated that patients with stones > 2 cm are less apt to be rendered stone free (Abdel-Khalek *et al.*, 2004). A multivariate study showed that the probability of being rendered stone free was 1.94 times higher for stones that were smaller than 15 mm. Others have convincingly shown that stones larger than 2 cm are less likely to be removed with SWL (Kim *et al.*, 2016).

B. Location: - regarding stone location, the greatest effects of ESWL are on stones that are, respectively, situated in the middle calyx, higher calyx, renal pelvis, and upper ureter. The latter sites, where the distal ureter and bladder are located, are less affected by ESWL.

C. hounsfield unit attenuation values and stone composition: -Stone attenuation measured on non-contrast tomography (NCCT) has been demonstrated to impact SWL results; this metric is quantified as Hounsfield units (HU) (Perks *et al.*, 2008), Pareek and associates assessed HU attenuation values as an independent predictor of SWL outcomes

(Pareek *et al*., 2005). The cut point for predicting failure is not clearly defined, but a liberal estimate is 1000 HU. A more conservative estimate would utilize an HU value of 750. These thresholds may be impacted by the type of lithotripter utilized, the lithotripsy techniques employed, and stone internal architecture. Wang and colleagues (Wang *et al*., 2005) study which involved patients with renal stones smaller than 2cm, the success rate for stones with an attenuation value of greater than 1,000 Hounsfield units was significantly lower than that for stones with a value of less than 1,000 Hounsfield units.

4-Lithotripter parameters: -

A. Shock waves rate: - One parameter that has been extensively studied is shock wave delivery rate, since stone breakage is related to shock wave rate (Mazzucchi *et al*., 2010).

Fragmentation of renal stones more efficient with slower shock wave delivery. According to the current leading hypotheses, a lower shock rate either reduces acoustic impedance mismatch or enhances the creation of cavitation bubbles on the surface of stones (Pace et *al*., 2005). This is because there is less water and gas surrounding the stone, which increases bubble dynamics.

With higher shock wave delivery rates, more cavitation bubbles build up on the stone's surface and are hypothesized to lessen the force of subsequent shock waves. Additionally, as the cavitation bubbles, which act as the cavitation nuclei, collapse, microbubbles are produced. This second possibility may result in "cavitation debris or bubble clouds," which would further diminish the delivery of shock wave energy. (Kekre and Kumar, 2008).

B. Power ramping up: - is another parameter related to stone sequence that has been shown to enhance renal stone comminution as well as minimize renal injury. This is because, when a stone receives a lot of energy at first, it breaks rather well, and a lot of small stone fragments build up in front of the remaining stone mass, potentially damping the subsequent shock waves. This barrier might be more effectively overcome by increased energy production at the end of the therapy as with a ramping-up procedure. The reno-protective effects of pretreatment are attributed to an increase in the renal vascular resistive index thought to be induced by constriction of renal blood vessels. (Nguyen *et al*., 2015).

C. Anesthesia: - Anesthetic technique may impact results; utilization of general anesthesia may result in better targeting and fragmentation, as the stone motion during respiration may affect the effectiveness of the ESWL (Sorensen *et al*., 2012).

D. Coupling techniques: - An air pocket reflects more than 99 percent of a shock wave. Owing to this, a coupling agent must be used to remove air from the space between the lithotripter's head and the patient. This will allow shock waves to be passed to the targeted calculus, a wide variety of coupling mediums were utilized, including creams, castor oil, petroleum jelly, ultrasonography gel, and other water-soluble lubricating jellies (Lingeman *et al*., 2009).

E. Shock wave delivery: - focal zone width, As the focal zone of the lithotripter gets smaller, the intensity of these shear waves decreases, and more tissue injury than narrow focal zone (Eisenmenger *et al*., 2002).

F. Dual-Heal Lithotripters: -Synchronous twin-pulse ESWL is promising, seems safe and effective for treating patients with renal and upper ureteric lithiasis (Sheir *et al* ., 2005), but some research revealed that when synchronized twin pulse shock waves were used, they caused more injury than single pulse conventional shock waves on renal tissue (Sheir *et al*., 2003).

2.3.6 Complications of ESWL

In comparison to other types of renal stone therapy techniques, ESWL has reportedly been shown to have a low mortality and low complication rate, also, complications of ESWL can be related disintegration and passage of fragments, infections, renal and nonrenal tissues effects.

2.3.6.1 Complications related to passage of fragments

Obstruction caused on by fragment passage occurs frequently temporarily and dissolves on its own, this occurs due to incomplete fragmentation, with remnant fragments of a significant size resulting in ureteral blockage (Steinstrasse ,German for stone street) which ends up with an obstruction of the urinary flow, the incidence of these complications is 6 to 20% (Al-Quorain, 2015).

There are a number of factors that have increased the risk of injuries related fragment passage, size, composition, the number of stones, and the frequency and strength of the shock wave (Yazici and ÜslÜmango, 2019).

Regarding the size , inversely related to the rate of safety and successful treatment , for stone less than 2 cm , the percentage of success reported, considered as "stone free rate," has been in the range of 66–99%, which drops to 45–70% for stones of 2-3 cm and even further again for staghorn stones, while stones >2 cm usually require multiple treatments and have higher risk of incomplete shattering ,with an incidence of partial obstruction between 19–50% (Sawal and Soebadi, 2020).

Also, some types of stones have higher risk of post ESWL complications, as they have a higher tendency to produce larger fragments that are resistant to shock waves, include dehydrated calcium phosphate stones (brushite) and monohydrate calcium oxalate stones.

Regarding lower pole renal stone, difficulty of passage fragments due to anatomical characteristic of this region may increase risk of post ESWL obstruction, often lower pole renal stone requires multiple treatment for clear up (Favorito, 2018).

The frequency and energy of shock waves is another risk factor that might contribute to incomplete fragmentation, since the potential of fragmentation is improved by a decrease in frequency, and a decrease in lesser volume pieces is correlated with an increase in the voltage applied (Nugroho, 2019).

2.3.6.2 Infectious complications

The renal trauma and vascular disruption associated With ESWL may increase the risk of infectious complications by allowing bacterial entrance into bloodstream from urine or infected stone itself, in 0.3% of patients (Wagenius *et al*., 2017).

Those with struvite stones, multiple or larger stone size (>2cm) stones, the presence of calyceal diverticula, or those who have undergone periprocedural stone or urologic manipulation have a higher incidence of developing clinical UTI (Oh *et al*., 2012).

The incidence of clinical urinary tract infections, asymptomatic bacteriuria, bacteremia and sepsis are 0.3%,2.8–5%, 5% and 1% respectively. The use of prophylactic antibiotic in high-risk patients may reduce the occurrence of post-ESWL infections (Capitanini *et al*., 2016).

2.3.5.3 Tissue effects of ESWL: -

A. Effect on kidney anatomy and function: -

The most obvious explanation of tissue kidney injury is hematuria, which usually resolves spontaneously within few days, Symptomatic intrarenal, subcapsular, or perirenal fluid collections and hematomas are rare and occur in <1% of patients who undergo ESWL. Early after treatment, the medium-sized arteries, veins, and glomerular capillaries in human kidneys were revealed to have endothelial cell injury through histopathological evaluation, thin-walled arcuate veins in the corticomedullary junction are especially susceptible to shock wave exposure and are associates to hematuria and haematoma (Jdaini *et al.*, 2020).

In regards as to how ESWL affects renal functions, biochemical evidence of renal injury is evident immediately after ESWL. Within a few days, blood and urine markers such renin, creatinine, N-Acetyl-bGlycosaminidase (NAG), b-galactosidase (BGAL), and proteinuria return to almost normal levels (Hegazy *et al.*, 2020).

Studies on humans show that, especially when pyelonephritis coexists, the glomerular filtration rate (GFR) and renal plasma flow are reduced shortly after ESWL. However, the effect of ESWL is short term, and resolves within few days, and this effect can be reduced by minimizing the voltage and number of shock waves (Konecki *et al.*, 2010).

B. Effect of ESWL on cardiovascular system

The association between SWL and arterial hypertension has long been a source of controversy and discussion.

About 8% of cases have had a diagnosis of hypertension following SWL, which is not significantly different from the incidence of roughly 6% of new diagnoses in the general population Additionally, an increase in diastolic pressure was observed following a SWL, and a connection between this and the quantity of shock waves was therefore hypothesized. Four years later, the annualized incidence of new onset hypertension in ESWL patients was 2.1%, compared to 1.6% in nonESWL patients (Wu *et al.,* 2021), However, the true cause of hypertension after ESWL is probably multifactorial, and whether there is a direct causal link is unclear. In addition, Renin-mediated or reninin dependent processes are more frequently responsible for affecting blood pressure. Recent research revealed that throughout a 24-month follow-up period, blood pressure was significantly increased by renal stone disease as opposed to the type of treatment (Mehrazin *et al*., 2011).

Regarding the effect of ESWL on heartbeat, Cardiac arrhythmias during ESWL are not uncommon, the incidence is 1l%–59%. They usually represent minor, unifocal premature ventricular contractions. while myocardial damage biomarkers or abnormal cardiac events are extremely uncommon (Mathers *et al*., 2015).

Extracorporeal shock wave lithotripsy may be performed safely on patients with pacemakers with appropriate precautions. Although the fact that a number of patients experienced abdominal aortic aneurysmal rupture during ESWL, experimental and clinical data indicate that patients with aortic and renal aneurysms can be treated effectively and without risks (Gugulakis *et al.*, 2003).

C. Effect of ESWL on gastrointestinal system

The most common extra-renal complications of ESWL are to the gastrointestinal system, several gastrointestinal lesions of various types have consistently been documented, with a global prevalence of 1.8% (Mata A *et al*., 2021).

These adverse effects were related to both the patient's position (increase in prone position) and the excessive number and power of shock waves given that exceeded the U.S. Food and Drug Administration (FDA) recommended numbers. Even though the specific pathophysiology is still unclear, cavitation, heat injury, and spallation are potential damaging mechanisms (Maker & Layke, 2004).

D- Effect of ESWL on pregnancy and fertility

There is adequate clinical and experimental evidence to exclude out any long-term impacts on ovarian or testicular function, thereby confirming that there is no association between SWL and fertility, However, due to any potential harm that shock waves could cause to the fetus, pregnancy is an only absolute contraindication to the procedure itself (Sayed, 2006).

3 Materials and methods

3.1 Materials.

3.1.1 Subjects.

This prospective cross-sectional study was directed on 50 patients (twenty-nine males and twenty-one females), Their age extended from (16-72) years, attending the ESWL treatment for the first time, the referrals of patients mainly from urologists, and from urologic outpatient department. The study was performed at the extra-corporeal shock wave lithotripsy unit (ESWL), AL-Hilla Teaching HospitaL, Babil province, and the biochemical investigation was carried out in postgraduate laboratories in college of medicine /university of Babylon, the study was from 1st of October /2021 to 30th of April 2022.

3.1.2 Inclusion criteria

All patients included in the research must diagnosed as have renal stone 0.8-2 cm confirmed by imaging modalities and undergo an Extracorporeal shock wave lithotripsy session for the first time.

3.1.3 Exclusion criteria

1- patients underwent ESWL session before.

2- Individuals with upper ureteric stone .

3- Patients with history of adrenal gland abnormality.

Ethical approval

All cases involved in this study were informed, and the consent was obtained verbally from each of them before the collection of samples. The study was approved by the committee of publication Ethics at College of

Medicine /University of Babylon according to the document number 7266 on 8/9/2021.

3.1.4 Instruments.

The instrument used in this study were presented in table (3-1):

Table (3-1): The instrument used in this study.

	Instruments	Company	Country
1	Lithotripter SLX-F2	Storz -medical	Switzerland
2	Ultrasound	Hitachi/prosound	Japan
3	Absorbance microplate reader ELx800	Biotek	U.S. A
4	Centrifuge	Ohaus	Switzerland
5	Blood glucometer	Rossmax	Switzerland
6	Incubator	Binder	U.S. A
7	Blood pressure and pulse rate monitor	Mindray	China
8	Deep freezer	Samsung	South korea

3.1.4.1 Extracorporeal shock wave lithotripsy machine: -

Modulith SLX-F2 lithotripter (electromagnetic) is used in this study for patients with renal stones and composed several components as shown in the figure (3-1)

- Therapy head (1)
- Basic unit (2)
- Control panel (3)

- Patient table (4)
- Image intensifier (5)
- X-ray application device (6)
- Ultrasonography (7)

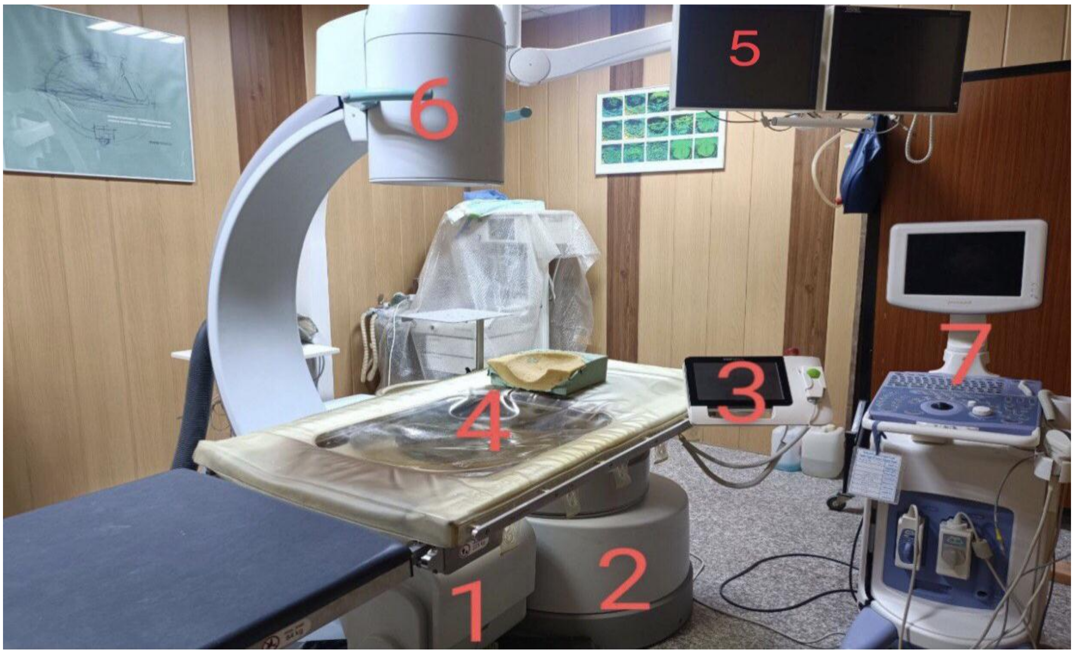

Figure (3-1): - ESWL machine used in this study

1-Therapy head

The system for shock wave generation, the therapy source, is in therapy head. And can be swiveled into different positions (park, treatment, and front positions).

2-Basic unit

The basic unit forms the base of the lithotripter and holds all components of the lithotripsy systems, the following items are installed in the basic unit.

- Electrical power supply

- Electronic control unit
- Shock wave generation and triggering system
- Water circuit
- Drive systems for moving the table and therapy head
- Connection socket for external devices\options

3-Control panel

The operating panel is located at the front side, attached to the standard rail .It can be removed and hooked into the standard rail at the head end. All important functions are available with fingertips and are easily distinguishable by their symbol and layout.

The treatment relevant shock wave parameters are permanently visible. The scrolling side menu shows the controls needed for the currently performed procedure keeping the user interface tidy and clear.

4-Patient table

The patient table is used for positioning of the patient during localization of stone and therapy applications.

5-X-ray applications device

Components belonging to the x-ray generator are mounted in C-arc: camera, image intensifier, collimator and x-ray tubes. the C-arc of the Xray system can be driven by motor from 0° to 30° position.

6-Ultrasonography

The ultrasound system integrated in lithotripter consists of the following components:

- Ultrasound inline module with transducer
- Ultrasound device
- Hand-held transducer

3.1.5. chemical material used in this study:

The chemical material used in this study were presented in table (3-2).

Table (3-2): - chemical material used in this study

	Chemical materials	Company	Country
1	Epinephrine kit (Adrenaline)	Elabscience	U.S. A
2	Norepinephrine kit	Elabscience	U.S. A
3	Dopamine kit	Elabscience	U.S. A

3.2 Methods

All subjects enrolled in the study undergo the history, clinical examination, biochemical tests, and ESWL session.

3.2.1. History

A detailed history was taken from each patient regarding demographic data like name, age, occupation, religion, address, daily life style (smoking, diet, exercise, Alcohol drinking), past medical history such as (hypertension, diabetic mellitus, kidney diseases and other chronic comorbidities), and history of previous ESWL, past surgical history focusing of surgery related to urinary system, history of medication. History of presenting illness focusing on symptoms related to urinary symptoms like (dysuria, frequency, hematuria, flank or loin pain).

3.2.2 Clinical examination

1- General examination and the vital signs of patients had been taken immediately before and after ESWL session, include (pulse rate, blood pressure, body temperature and respiratory rate).

2-Body mass index (BMI).

Each patient body mass index (BMI) was calculated by evaluation the weight in kilogram and the height in meter, then after the weight is divided by height squared (kg/m^2) to obtain BMI (Bottcher *et al*.,2020).

The study group were divided according to world health organization (WHO), which classified body mass index into underweight (below 18.5 kg/m^2), normal (18.5-24.9 kg/m^2), pre-obese (25-29.9 kg/m^2), obesity class 1 (30-34.9 kg/m^2), obesity class 2 (35-39.9 kg/m^2) and obesity class 3 $\geq$ 40 kg/m^2.

Table (3.3) : Questionnaires used in this study

Pat.code () Name:- sex ( )	
Weight () kg height () cm Age( ) years	
Address rural () urban ( )	
Occupation () religion ( )	
Educational status; Illiterate () primary school ( ) Secondary school () University ()	
Past medical history: -	drug history: -
Past surgical history: -	family history:
social history: -	clinical presentation: -
According to imaging modalities (ultrasound, Ct scan): - Site of renal stone: - upper calyceal (), mid calyceal (), lower calyceal () No. of renal stones: - single (), multiple (). Stone opacity: - opaque (), lucent ()	
Power of shock waves: - No. of shock waves: -	Frequency of shock waves: - Duration of ESWL session: -
Blood pressure: - pre_session () MmHg, post_session ( )MmHG Pulse rate: - pre-session () bpm, post-session ( ) bpm. Body temperature: - pre-session () °C, post-session () °C. Respiratory rate: - pre-session () Rpm, post-session () Rpm.	

3.2.3 biochemical tests.

3.2.3.1 measurement of serum catecholamine level as following: -

3.2.3.1.1 blood collection.

A venous blood (4-5 milliliters) sample was drawn from each patient by using a disposable syringe and immediately placing it in a Gel tube and Allow samples to clot for 1 hour at room temperature before centrifugation for 20 min at 1000×g at 2-8℃. Collect the supernatant to carry out the assay.

1-Epinephrine kit: -

Employed an epinephrine kit to quantify the amount of epinephrine in the serum of patients before and after ESWL session (Human Epinephrine/Adrenaline ELISA Kit, USA).

Principle: This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with human EPI antibody. EPI present in the sample is added and binds to antibodies coated on the wells.

Then biotinylated human EPI Antibody is added and binds to EPI in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated EPI antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added, and color develops in proportion to the amount of human EPI. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm which is proportional to the epinephrine level in the sample.

Figure (3-3): Epinephrine kit used in this study.

2-Norepinephrine kit

By using norepinephrine kit for measurement of serum nor_e pinephrine level before and ESWL session.

Principle: - This ELISA kit uses Competitive-ELISA as the method. The microtiter plate provided in this kit has been pre-coated with NA/NE. During the reaction, NA/NE in the sample or standard competes with a fixed amount of NA/NE on the solid phase supporter for sites on the Biotinylated Detection Ab specific to NA/NE. Excess conjugate and unbound sample or standard are washed from the plate, and Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated.

TMB substrate solution is added to each well. The enzyme-substrate reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of NA/NE in the samples is then determined by comparing the OD of the samples to the standard curve.

3- Dopamine kit: -

Used a dopamine kit to measure the level of dopamine in patients' serum both before and after an ESWL session.

Principle: - This ELISA kit uses the Competitive-ELISA principle. The micro-ELISA plate provided in this kit has been pre-coated with DA. During the reaction, DA in the sample or standard competes with a fixed amount of DA on the solid phase supporter for sites on the Biotinylated Detection Ab specific to DA. Excess conjugate and unbound sample or standard are washed from the plate, and Avidin conjugated to Horseradish Peroxidase (HRP) are added to each microplate well and incubated.

TMB substrate solution is added to each well. The enzyme-substrate reaction is terminated by the addition of stop solution and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The concentration of DA in the samples is then determined by comparing the OD of the samples to the standard curve.

Figure (3-4): Dopamine kit used in this study

3.2.3.1.2 Reagent preparation

A- Reagent preparation for Dopamine and Epinephrine kit

All reagents were brought to room temperature (18-25℃) before use and 750 ml of wash buffer was prepared by diluting 30 ml of Concentrated Wash Buffer with 720 mL of deionized or distilled water. in the next step, the Standard working solution was prepared by

Centrifuging the standard at 10,000×g for 1 min and adding 1.0 ml of reference standard & sample diluent then stood for 10 min and inverted gently several times then mixed thoroughly with a pipette.

This reconstitution produced a working solution of 2000 pg/mL. in the dilution method, 500uL of Reference Standard & Sample Diluent was added to 7 EP tubes then 500Ul of the 2000 pg/mL working solution was Pipetted to the first tube and mixed up to produce a 1000 pg/mL working solution and 500uL of the solution from the former tube was Pipetted into the latter one.

Then Biotinylated Detection Ab working solution was prepared by Calculating the required amount before the experiment (50 μL/well). Centrifuging the Concentrated Biotinylated Detection Ab at 800×g for 1 min, then diluting the 100× Concentrated Biotinylated Detection Ab to 1× working solution with Biotinylated Detection Ab Diluent.

The final step was Concentrated HRP Conjugate working solution preparation by Calculating the required amount before the experiment (100μL/well) then the Concentrated HRP Conjugate Centrifuged at 800×g for 1 min, then diluted the 100× Concentrated HRP Conjugate to 1× working solution with HRP Conjugate Diluent.

B- Reagents preparation of Norepinephrine kit

All reagents were brought to room temperature (18-25℃) before use and 750 ml of wash buffer was prepared by diluting 30 ml of Concentrated Wash Buffer with 720 mL of deionized or distilled water. in the next step, the Standard working solution was prepared by Centrifuging the standard at 10,000×g for 1 min and adding 1.0 ml of reference standard & sample diluent then stood for 10 min and inverted gently several times then mixed thoroughly with a pipette.

This reconstitution produced a working solution of 20 ng/mL. in the dilution method, 0.5 mL of Reference Standard & Sample Diluent was added to 7 EP tubes then 0.5 mL of the 20 ng/mL working solution was Pipetted to the first tube and mixed up to produce a 10 ng/mL working solution and 0.5 mL of the solution from the former tube was Pipetted into the latter one.

Then Biotinylated Detection Ab working solution was prepared by calculating the required amount before the experiment (50 µL/well). The concentrated Biotinylated detection Ab was centrifuged and diluted to the working solution by Biotinylated Detection Ab Diluent (1:100). The final step was the Concentrated HRP Conjugate working solution prepared by Calculating the required amount before the experiment (100µL/well) then the Concentrated HRP then diluted to the working solution by HRP Conjugate Diluent (1:100).

3.2.3.1.3 Eliza procedure for measurement of serum catecholamine level

Wells were Determined for diluted standard, blank and sample. 50 µL was Added for each dilution of standard, blank and sample into the appropriate wells. Immediately 50 µL of Biotinylated Detection Ab working solution was added to each well. then the plate was Covered with the sealer provided in the kit and incubated for 45 min at 37°C.

The solution from each well was Decanted and 350 µL of wash buffer was added to each well then soaked for 1 min and the solution was aspirated from each well and patted until became dry against clean absorbent paper. this step was Repeated 3 times. the next step was Adding 100 µL of HRP Conjugate working solution to each well and covering the plate with a new sealer then Incubated for 30 min at 37°C then the wells were washed and decanted for 5 times. 90 µL of Substrate Reagent was

Added to each well and Covered with a new sealer then Incubated for about 15 min at 37°C.

The final step, 50 µL of Stop Solution was Added to each well and optical density (OD value) was Determined for each well at once with a micro-plate reader set to 450 nm.

Figure (3-5): -Absorbance microplate reader ELx800 used.

3.2.3.2 Measurement of blood glucose

The level of blood glucose of patients before and after ESWL session was measured immediately by using electronic blood glucometer, by applying drop of blood to a chemically treated disposable test strip, he reaction between the test strip and the blood is detected by the meter and displayed in units of mg/dL.

3.2.4 ESWL session: -

The treatment for patients with renal stone by using shock wave was done at ESWL unit at Al-Hillla teaching hospital using modulith SLX-F2 lithotripter.

3.2.4.1 Patient preparation for ESWL

-Patients were advised to stop eating or drinking two to four hours before the procedure and to stop smoking if they smoked, Caffeine containing foods and beverages, such as coffee, tea, or cola, must be avoided before the procedure.

-Drugs such as aspirin-containing medications, anticoagulants, platelet inhibitors, non-steroidal anti-inflammatory should be discontinued seven to ten days before session as it may increase of post-ESWL bleeding.

-Documentation of a negative urine culture is essential of post_ procedural urinary tract infection or sepsis.

-Patients were given analgesia 30 to 60 minutes prior to ESWL session to reduce pain sensation, so decrease patient movement during the procedure and thus promote stone degradation.

-Initial imaging documents that confirm the presence of stone (no., site, size, radiopacity of stone), and also detect if there is any urinary tract obstruction.

-In women of childbearing age, a pregnancy test is administered before session as there is risk of radiation exposure.

-Patients may be advised to drink clear liquids, take a laxative, or both the day before the procedure depending on the size, radiopacity, and location of the stone so that visualization of the stone can be enhanced by a reduction in overlying stool and bowel gas.

-The patient ought to be informed of any potential consequences and failure risks.

-Positioning of patient: -In specialized treatment room, which has the shock wave machine and imaging equipment, position dictated by the location of the stone. The supine position of patients was used in this study, for accurate localization of renal stone., so that the stone is located approximately above the focal point.

3.2.4.2 The procedure of ESWL

The ESWL procedure takes about 20-30 minutes, and sometimes longer depending on the size and number of the stones. During the procedure**.**

-Stone localization: - the stones to be treated are moved to the treatment focus using the localization system, An X-ray and/or a supplied ultrasound system can be used for this, and by movement of the table until the stone lies within the focal point.

-Setting shock waves parameter (energy, frequency and number of shock waves), adjustment of ESWL parameter usually depend on the size, composition of the stone, as well as appearance of the stone as treatment progresses , figure (3-6) generation of shock waves by lithotripter .

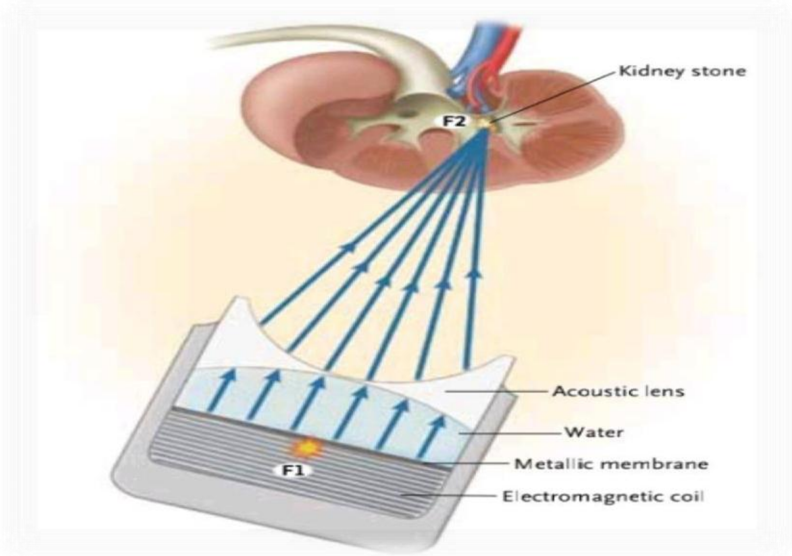

Figure (3-6) Electromagnetic Lithotripter

-ESWL session ,is performed on an out-patient basis with no need for hospital admission following the procedure, At the time of discharge, patients are given a prescription for analgesics and a strainer to collect stone fragments during voiding for later analysis.

-After the procedure, patients are instructed to watch for signs of infection or obstruction as stone fragments are passed. A few days of mild hematuria and flank soreness can be expected, and the patient ought to be informed of that previously, but persistent, heavy, gross hematuria or severe pain should prompt a reevaluation and an assessment for bleeding complications.

Table (3-4): normal value of biochemical tests (Diabetes UK, 2019) (Guber *et al*., 2017).

Test	Normal range
Blood glucose	Fasting: 72 to 99 mg/dL 2 hours after meal: up to 140 mg/dL
Dopamine	0 to 30 pg/mL
Epinephrine	0 to 140 pg/mL
Norepinephrine	70-1700 pg/ml

3.3 Data Analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student t-test was used to compare means between two groups. Paired t-test was used to compare means for two paired readings. Analysis of variance (ANOVA) test was used to compare means between three groups or more. Pearson's correlation coefficient (r) was used to find the relationship between two continuous variables. A *p*-value of < 0.05 was considered as significant.

4 Results

4.1 The distribution of patients according to socio-demographic characteristics

4.1.1 The distribution of patients according to age and gender

Table (4.1) shows distribution of patients according to socio-demographic characteristics including (age /years, gender). There were 32% of patients their ages ranged between (30-40 years), Mean age of patients was (44.40 ± 13.56) with maximum age was (72.00) years and minimum age was (16.00) years, more than half of patients were males (N=29, 58.0%).

Table (4.1): The Distribution of patients according to age and gender (N=50)

Study Variables	Number	%
Age (years)		
< 30	4	8.0%
30-40	16	32.0%
40-50	12	24.0%
50-60	10	20.0%
60-70	6	12.0%
≥ 70	2	4.0%
Total	50	100.0%
Gender		
Male	29	58.0%
Female	21	42.0%
Total	50	100.0%

4.1.2 Distribution of patients according to body mass index (BMI) (kg/m^2).

Mean BMI of patients was (29.05 ± 4.48 kg/m^2) with maximum BMI was 43.30 kg/m^2 and minimum BMI was 20.80 Kg/m^2.Table (4.2).

Table (4.2): distribution according to Body Mass Index (kg/m^2)

Body mass index (kg/m^2)	Number	%
Normal (18.5-24.9)	8	16.0%
Overweight (25-29.9)	23	46.0%
Obese (≥ 30)	19	38.0%
Total	50	100.0%

4.1.3 Distribution of patients according to living address and occupation

As seen in figure below (4.1), a total of 33 patients resided in urban areas with a frequency of 66.0%, while 17 patients did so in rural areas with a frequency of 34%. According to figure (4.2), 35 patients (65%) of employed.

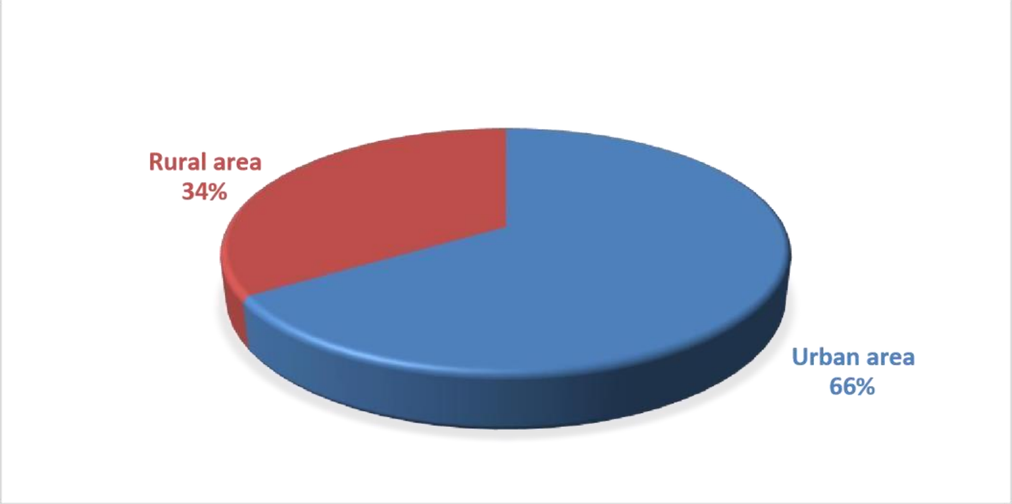

Figure (4.1): Distribution of patients according to living address

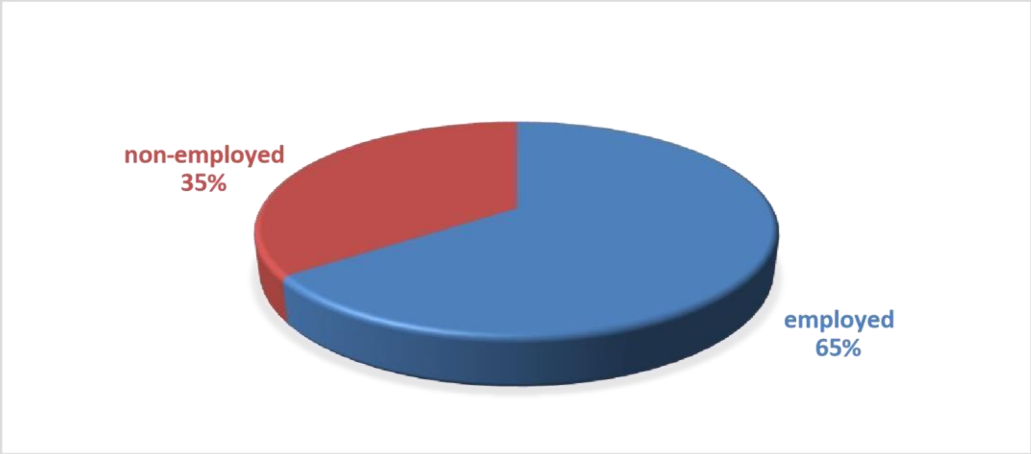

Figure (4.2): Distribution of patients according to occupation

4.2 Distribution of patients according to clinical characteristic

4.2.1 Distribution of patients regarding past medical history

Table (4.3) displays the distribution of patients based on their past medical history, including their history of renal stones, hypertension, and diabetes mellitus (positive and negative). (N=33, 66.0%) of all patients have a positive past medical history.

Table (4.3): The Distribution of patients according to past medical history (N=50)

Study variables	Number	%
Past medical history		
Positive	33	66.0%
Negative	17	34.0%
Total	50	100.0%
Type of disease		
Hypertension	6	18.2%
Diabetes mellitus	4	12.1%
Renal stone	24	48.5%
More than one type of disease	16	21.2 %
Total	50	100 %

4.2.2 Distribution of patients regarding family history of renal stone

Regarding family history of renal stone, there were 28 (56%) of patient having a positive family history of renal stone disease as displayed in table (4.4).

Table (4.4): distribution of patients according to family history of renal stone disease.

Study variable	Number	%
Positive family history of renal stone	28	56 %
Negative family history of renal stone	22	44%
Total	50	100%

4.2.3 Distribution of patients according to renal stone characteristic.

Table (4.5) shows distribution of patients according to stone characteristics including (site, number and type).

Sixty percent (N=30) of patients presented with stone in lower pole, 78.0% of them (N=39) presented with single stone, regarding stone opacity 70% of stones were radiopaque.

Table (4.5): The Distribution of patients according to stone characteristics (N=50)

Stone characteristics	Number	%
Stone site		
Lower pole	30	60.0%
Mid pole	9	18.0%
Upper pole	11	22.0%
Total	50	100.0%
Stone number		
Single	39	78.0%
Multiple	11	22.0%
Total	50	100.0%
Stone opacity		
Opaque	35	70.0%
Lucent	15	30.0%
Total	50	100.0%

4.2.4 Distribution of patients according to parameters of lithotripter.

Table (4.6) shows distribution of patients according to parameter of lithotripter used in this study, including (number of shock wave, power (energy KV) and frequency (hz). Mean shock wave was (2700.0 ± 462.91) with minimum number was (1500) and maximum number was (3000).

Regarding energy, half of patients (N=25, 50.0%) take dose of (5-7 KV), 84 % of patients (N=42) undergone treatment with frequency 1.5 hz.

Table (4.6): The Distribution of patients according to characteristics of ESWL (N=50)

Parameter	**Mean SD ±**	**Range**
Number of shock wave	(2700.0 ± 462.91)	(1500-3000)
Parameter	**NO.**	**Range**
Energy KV		
2 and 2.5	4	8.0%
3 and 3.5	10	20.0%
4 and 4.5	11	22.0%
5, 6 and 7	25	50.0%
Total	50	100.0%
Frequency (hz)		
1.5	42	84.0%
2.0	7	14.0%
3.0	1	2.0%
Total	50	100.0%

4.2.5 The distribution of patients according to blood pressure measurement (mmHg)

There were significant differences between the mean differences of systolic and diastolic blood pressure (mmHg) prior ESWL and then after, (p value <0.001), as shown in table (4.7).

Table (4.7): The mean differences of systolic and diastolic blood pressure between two periods of assessment (pre and post) ESWL

Study variables	Periods of assessment	Mean ± SD	Pvalue
Systolic blood pressure (mmHg)	Pre ESWL	126.60 ± 18.14	**<0.001****
	Post ESWL	142.40 ± 16.23	
Diastolic blood pressure (mmHg)	Pre ESWL	76.20 ± 9.45	**<0.001****
	Post ESWL	80.50 ± 7.71	

* Significant, ** highly significant

4.2.6 Distribution of patients according to pulse rate (per minute) reading

The mean differences of pulse rate /minute, pre ESWL and post ESWL session are significantly changes with (p value <0.001), as seen in table (4.8)

Table (4.8): The mean differences of pulse rate (per minute) between two periods of assessment (pre ESWL and post ESWL)

Study variables	Periods of assessment	Mean ± SD	P value
Pulse /minute	Pre ESWL	90.06 ± 10.09	<0.001**
	Post ESWL	98.88 ± 12.84	

* Significant, ** highly significant

4 .3 Distribution of patients according to biochemical investigations

4.3.1 Distribution of patients according to blood glucose level

The mean differences ± SD of blood glucose level (mg/dl) between two periods of assessment including (pre and post ESWL session) were 109.76 ± 52.42 and 123.46 ± 54.19 respectively, which was highly significant (p value <0.001) as shown in table (4.9).

Table (4.9): The mean differences of blood glucose level (mg/dl) between two periods of assessment (pre and post) ESWL

Study variables	Periods of assessment	Mean ± SD	P value
RBS (mg/dl)	Pre ESWL	109.76 ± 52.42	**<0.001****
	Post ESWL	123.46 ± 54.19	

* Significant, ** highly significant

4.3.2 Distribution of patients according to serum epinephrine level

Table (4.10) illustrated the mean differences in epinephrine level (pg/ml) between two measurement periods (pre and post) session, with highly significant differences as p value <0.001.

Table (4.10): The mean differences of epinephrine (pg/ml) between two periods of assessment (pre ESWL and post ESWL) session.

Study variables	Periods of assessment	Mean ± SD	P value
epinephrine (pg/ml)	Pre ESWL	3.945 ± 2.758	**<0.001****
	Post ESWL	9.452 ± 5.503	

* Significant, ** highly significant

4.3.2.1 Relationship between serum epinephrine level post ESWL and energy of lithotripter (KV)

Table (4-11) demonstrated the relationship between serum epinephrine level post ESWL session and the used energy (KV) of lithotripter, with no significant relationship as (p value>0.05).

Table (4.11): The mean differences of epinephrine (pg/ml) according to power (energy KV).

variables	Energy /KV	N	Mean ± SD	P-value
Epinephrine post ESWL (pg/ml)	2 and 2.5	4	11.920 ± 3.924	>0.05
	3 and 3.5	10	9.379 ± 6.981	
	4 and 4.5	11	7.589 ± 4.997	
	5 and 6 and 7	25	9.905 ± 5.328	

* Significant, ** highly significant

4.3.2.2 Relationship between serum epinephrine level post ESWL and frequency of lithotripter

The relationship between frequency (hz) including (1.5 or 2 and 3) of lithotripter and post session serum epinephrine are displayed in table (4.12), which revealed that there were no significant differences with ($p>0.05$).

Table (4.12): The mean differences of epinephrine (pg/ml) post ESWL according to frequency (hz)

Study variables	Frequency (hz)	N	Mean ± SD	P-value
Epinephrine post ESWL (pg/ml)	1.5	42	8.946 ± 5.404	>0.05
	2 and 3	8	12.107 ± 5.597	

* Significant, ** highly significant

4.3.2.3 The Correlation between mean differences of serum epinephrine level post ESWL (pg/ml) and number of shock wave

The correlation between serum epinephrine level post ESWL (pg/ml) and the number of shock waves of lithotripter are shown in figure (4.3), which demonstrated that there was no significant linear correlation (N=50, r= - 0.23, P=0.109).

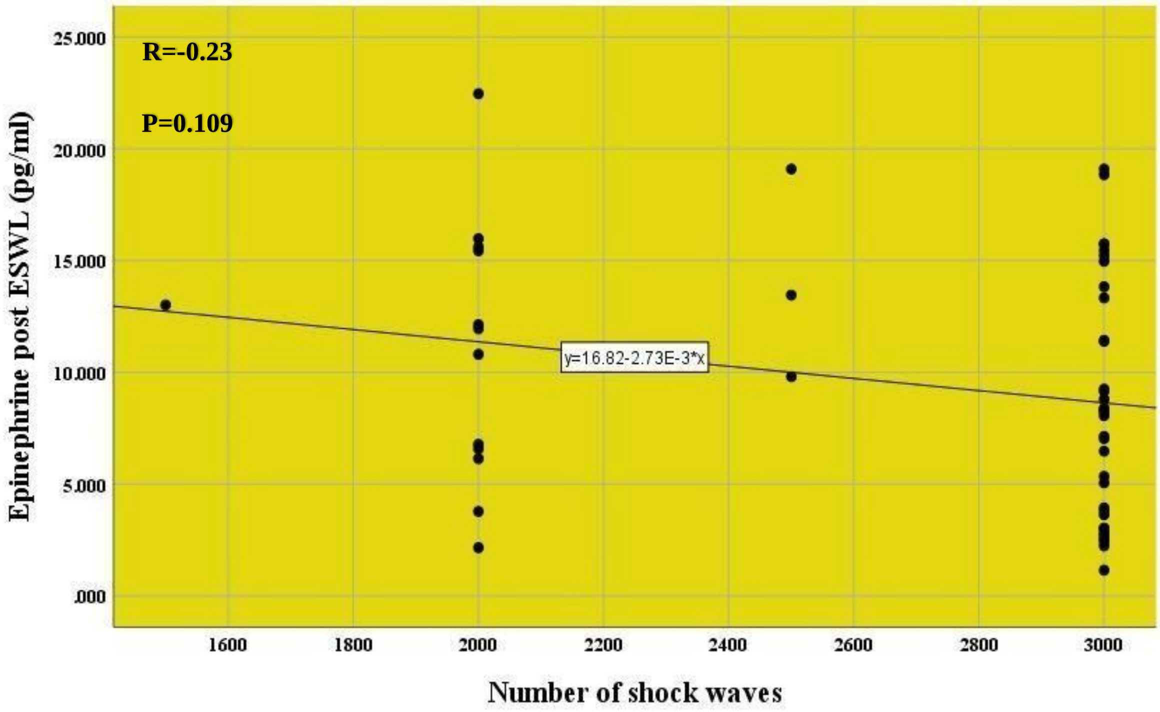

Figure (4.3): The correlation between Epinephrine post ESWL (pg/ml) and number of shock waves among study patients (N=50, r= -0.23, P=0.109)

4.3.2.4 Relationship between epinephrine level post ESWL and site of renal stone

There was a significant relationship between means of epinephrine level post ESWL session according to site of stone (lower, mid and upper) pole with (p value < 0.05) as shown in table (4.13).

Table (4.13): The mean differences of Epinephrine (pg/ml) post ESWL according to site of stone

variables	Site of stone	N	Mean ± SD	P-value
Epinephrine post ESWL (pg/ml)	Lower pole	30	8.281 ± 5.277	**<0.05***
	Mid pole	9	7.739 ± 3.631	
	Upper pole	**11**	**14.047 ± 5.206**	

* Significant, ** highly significant

4.3.3 Distribution of patients according to serum norepinephrine level pre and post ESWL session.

Table (4.10) demonstrated the mean differences in norepinephrine level (pg/ml) between two measurement periods, including (pre and post) session, with highly significant differences as p value <0.001.

Table (4.14): The mean differences of norepinephrine (pg/ml) between two periods of assessment (pre ESWL and post ESWL)

variables	Periods of assessment	Mean ± SD	P value
Norepinephrine (pg/ml)	Pre ESWL	73.945 ± 2.758	**<0.001****
	Post ESWL	176.420 ± 48.610	

* Significant, ** highly significant

4.3.3.1 Association between serum norepinephrine level (pg/ml) post ESWL and energy (KV) of lithotripter

As displayed in table (4.15), there were no significant association between mean differences of serum norepinephrine level post ESWL and changes of energy of lithotripter (KV), p value >0.05.

Table (4.15): The mean differences of norepinephrine level (pg/ml) post ESWL according to power (energy KV)

variables	Energy /KV	N	Mean ± SD	P value
Norepinephrine post ESWL (pg/ml)	2 and 2.5	4	165.669 ± 34.545	
	3 and 3.5	10	171.925 ± 49.149	

	4 and 4.5	11	192.995 ± 62.067	>0.05
	5 and 6 and 7	25	192.645 ± 44.098	

* Significant, ** highly significant

4.3.3.2 Association between serum norepinephrine (pg/ml) level post ESWL and frequency of lithotripsy

On the other hand, the mean differences of serum norepinephrine level (pg/ml) statistical not significant associate with the frequency (hz) of lithotripter, as p value >0.05, which shown in table (4.16).

Table (4.16): The mean differences of norepinephrine (pg/ml) post ESWL according to frequency (hz)

Study variables	Frequency (hz)	N	Mean ± SD	P value
Norepinephrine post ESWL (pg/ml)	1.5	42	187.871 ± 49.297	>0.05
	2 and 3	8	178.804 ± 47.200	

* Significant, ** highly significant

4.3.3.3 Correlation between mean differences of post ESWL serum norepinephrine level and number of shock waves

There was no significant linear correlation between norepinephrine level and the number of shock waves (p value >0.05), as shown in figure (4.4). (N=50, r= - 0.131, P=0.364).

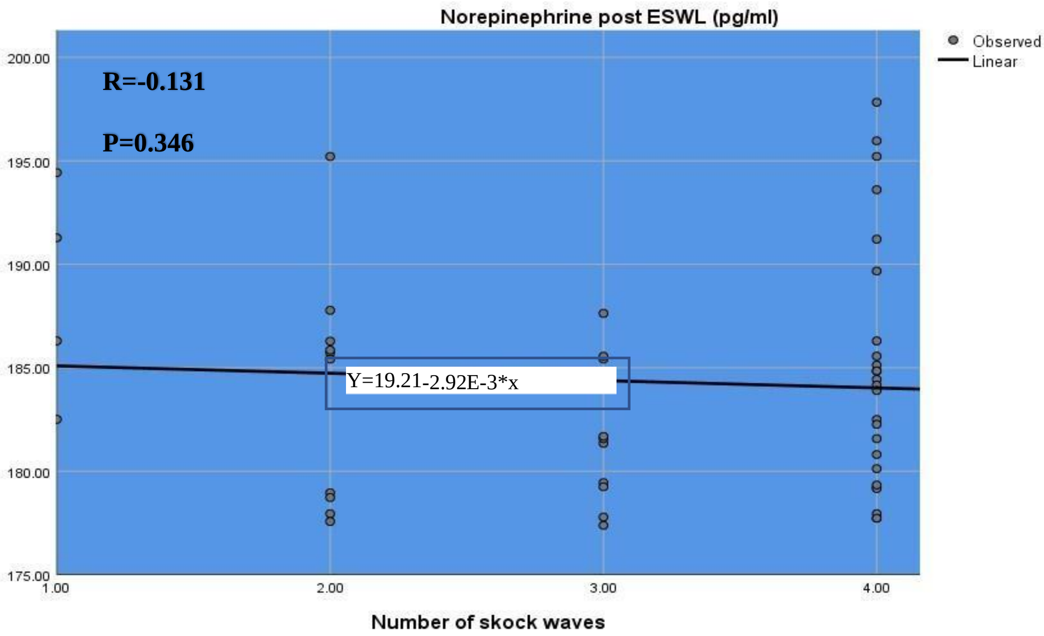

Figure (4.4): The correlation between norepinephrine level post ESWL (pg/ml) and number of shock waves among study patients (N=50, r= -0.131, P=0.364)

4.3.3.4 Relationship between serum norepinephrine level post ESWL (pg/ml) according to site of renal stone

On trying to make association between serum norepinephrine level following ESWL according to the site of renal stone among patients of our study, we found this association to be a significant as there are considerable differences in the level of serum norepinephrine across different site of renal stone (p value <0.05) as displayed in table (4.17).

Table (4.17): The mean differences of norepinephrine level (pg/ml) post ESWL according to site of stone

variables	Site of stone	N	Mean ± SD	P-value
Norepinephrine post ESWL (pg/ml)	Lower pole	30	183.531 ± 5.590	**<0.05***
	Mid pole	9	182.547 ± 3.438	
	Upper pole	**11**	**187.963 ± 5.331**	

* Significant, ** highly significant

4.3.4 Distribution of patients according to serum dopamine level (pg/ml)

There was a significant mean difference in the level of serum dopamine (pg/ml) between the two measurement periods (pre and post ESWL session) with p value <0.001, as illustrated in table (4.18)

Table (4.18): The mean differences of dopamine (pg/ml) between two periods of assessment (pre ESWL and post ESWL)

Variables	Periods of assessment	Mean ± SD	P-value
Dopamine (pg/ml)	Pre ESWL	1.169 ± 0.036	**<0.001****
	Post ESWL	2.381 ± 0.861	

* Significant, ** highly significant

4.3.4.1 Association between serum dopamine level (pg/ml) and energy (KV) of lithotripter

On trying to manifest the association of serum dopamine level post ESWL and energy of lithotripter including (2 and 2.5, 3 and 3.5, 4 and 4.5 and 5, 6 and 7), the mean levels of serum dopamine did not prove a statistically significant differences in correlation to change in power of lithotripter (KV) with p value >0.05.

Table (4.19): The mean differences of dopamine (pg/ml) post ESWL according to power (energy KV)

Study variables	Energy KV	N	Mean ± SD	P-value
Dopamine post ESWL (pg/ml)	2 and 2.5	4	2.549 ± 0.743	>0.05
	3 and 3.5	10	2.519 ± 1.069	
	4 and 4.5	11	2.056 ± 0.835	
	5 and 6 and 7	25	2.441 ± 0.813	

* Significant, ** highly significant

4.3.4.2 Relationship of post ESWL dopamine level and frequency of lithotripter (hz).

The study attempted to demonstrate how changes of frequency of lithotripter (hz) can affect the level of dopamine level post ESWL, as displayed in table (4.20) below, there was no significant differences (p value >0.05).

Table (4.20): The mean differences of dopamine (pg/ml) post ESWL according to frequency (hz)

variables	Frequency (hz)	N	Mean ± SD	P-value
Dopamine post ESWL (pg/ml)	1.5	42	2.367 ± 0.853	>0.05
	2 and 3	8	2.453 ± 0.961	

* Significant, ** highly significant

4.3.4.3 Correlation between post ESWL dopamine level and number of shock waves

Figure (4.5) shows the relationship between the number of shock waves of lithotripter and dopamine level post-ESWL (pg/ml), where there was no significant correlation (N=50, r=-0.135, P=0.351).

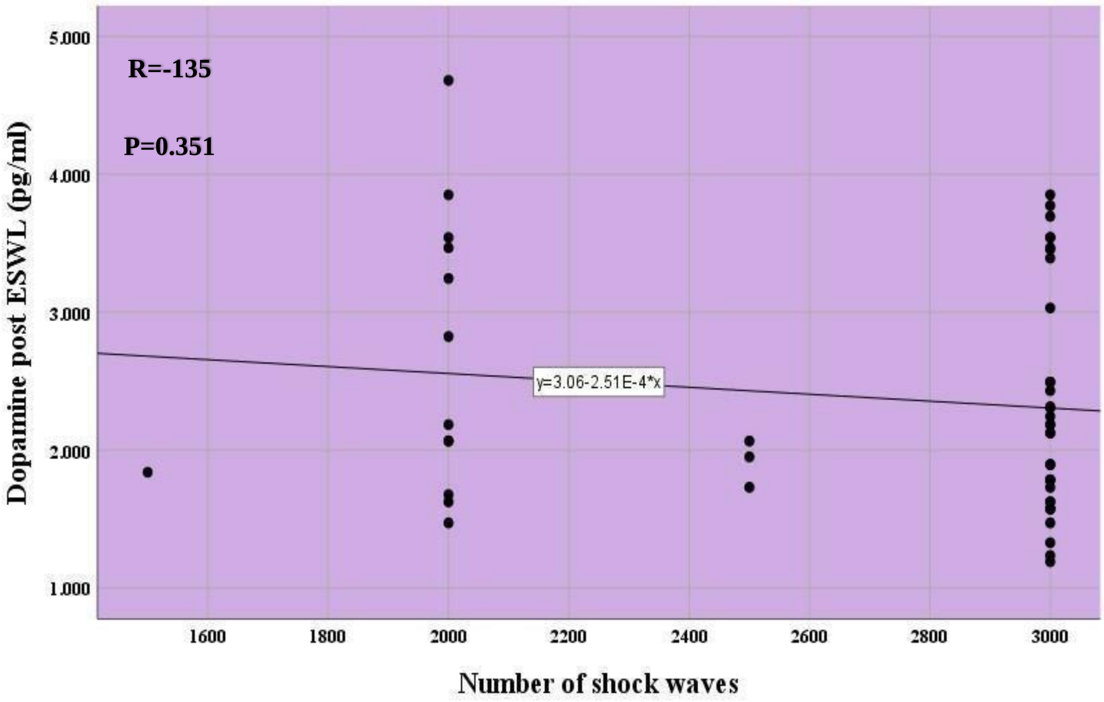

Figure (4.5): Correlation between dopamine post ESWL level (pg/ml) and number of shock waves among study patients (N=50, r = -0.135, P=0.351)

4.3.4.4 Association between serum dopamine level (pg/ml) post ESWL and site of renal stone.

According to stone location, there was no significant differences in post-ESWL dopamine level (pg/ml), as p value >0.05.

Table (4.21): The mean± SD of **dopamine level (pg/ml) post ESWL according to site of stone**

Study variables	Site of stone	N	Mean ± SD	P-value
Dopamine post ESWL (pg/ml)	Lower pole	30	2.529 ± 0.913	>0.05
	Mid pole	9	2.115 ± 0.583	
	Upper pole	11	2.191 ± 0.879	

* Significant, ** highly significant

5 Discussion

5.1 Demographic characteristic

The high rise in incidence of renal stones amongst people in the Eastern Mediterranean region including Iraq may be related to weather, stress, water intake, diet, genetics, socio-cultural habits.

In our country, extreme weather conditions are associated with a higher risk of kidney stone formation, as the incidence of crystallization and the formation of stones is enhanced by increased sweating, which resulting in risen of urine concentration. Decrease of urine pH value also during the last twenty years as the standard of living in Iraq has risen, with this socioeconomic change, the Iraqi diet has changed, there is more consumption of high protein (red meat) diet which leads to increase purine load and subsequently hyperuricemia (Silva Linhares *et al*., 2018),

Alkhayal *et al* (2021), presented in their review that the prevalence of renal stones in Saudi Arabia was 16.40%, so because both countries share the same climatic conditions and cultural habits, the prevalence of renal stones in Iraq is somewhat similar to that of the neighboring country of Saudi Arabia.

5.1.1. Distribution of patients according to age

The highest prevalence of renal stones reported in this study was in the age group 30–40 years (32%), as shown in table (4-1).

Regarding the factor of age, noted a pattern where the highest frequency of developing renal stones was when the patient was at the peak of his or her career. The results agreed with Popov *et al*., (2021) study which was included 14 countries in, including Iraq, where the average age was 48 (±14) years. On the other hand, an international study in united states America founded by Katz *et al*., (2021), revealed that the overall prevalence of urinary stones appears to rise linearly with age, peaking between 60 and 70 years. Previous research in Europe, a German study by Knoll *et al*., (2010), found that individuals in their 40 to 49 years, who were middle-aged had a propensity toward an increasing incidence of renal stones, which is almost similar to the result obtained from our study. The results Confirms the hypothesis that dietary habits, metabolic rate and lifestyle could be risk factors for renal stones (Fadhil, 2022)

5.1.2 Distribution of patients according to gender

In terms of gender, 58% of the patients in our study was male, with a male to female ratio of 1.38:1 table (4.1). The current study's male to female ratio is close to Karabacak *et al*., (2013), a multinational research involving the Iraqi population, which found a male to female ratio of 1.57:1. Males are more likely than females to get kidney stones, which could be explained by a number of variables , males tend to consume more protein (red meat) in their diets than women, that’s increases their risk of developing kidney. Contrarily, estrogen in women causes them to produce a copious amount of citric acid, which decreases the risk of kidney stone formation (Akram, 2019).

5.1.3 Distribution of patients according to body mass index body

In terms of basal metabolic rate, it was discovered that the mean BMI of patients in this study was (29.05 ± 4.48 kg/m^2), as displayed in table (4.2). This indicates that more than two thirds of patients are either overweight (25–29.9 kg/m^2) or obese (≥ 30) kg/m^2).

Regarding the countries neighboring Iraq, in the Jordanian population, Abu Ghazaleh and Budair (2013), in their study, concluded that there is a clear relationship between obesity and stone formation.

Similar to our result, Alghamdi, and his co-worker (2018), in their research which conducted in Saudi Arabia, an increase body mass index plays a major role in the development of urinary stones.

An explanation for this outcome, elevated body mass index plays an essential role in kidney stone formation, one reasoning for the rise in the prevalence of kidney stones in overweight people may be related to those patients' bad dietary habits, such as consuming more protein, more carbohydrates and less fiber intake, as well as their lifestyle behaviors. Also, higher BMI promotes urinary excretion of calcium, uric acid and oxalate, thereby participating in stones formation. A lower urinary volume with lower urinary pH and lower excretion of citrate was also documented as a cause of increased risk factor in obese stone formers, these causes increased excretion of urinary lithogenic substances. Diabetes mellitus type 2 and the metabolic syndrome are more common in obese persons. As a result, they are more vulnerable to develop renal stone (Poore *et al.*, 2020).

5.1.4 Distribution of patients according to living address and occupation

In this study, 66% of the patients lived in urban rather than rural areas (figure 4.1), the reason for this ratio is people's awareness and education have increased in those area in compared with patients in rural areas, they are more likely to visit a clinic for a checkup and to pay attention to their health , It's may also be related to the weather and the types of food that people eat.

Additionally, more than half of the study's patients were employed, as in figure (4.2), which may be cultural given that the majority of participants were men and that in Iraqi society, men were expected to work hard and provide for their families, workouts can raise the risk of developing kidney stones because they make people sweat more and produce less urine, which lowers pH and causes stones to form (Kuźma *et al* ., 2021).

That’s agreed with Robertson’s study (2012) ,that included urban societies in Oil-rich Gulf countries , he found that the chance of having both UA- and CaOx containing stones will unquestionably increase, and the most obvious cause as ,most urban communities in these countries live in hotter environments and so the loss of fluid through sweating rather than urination , leading to decrease urine volume.

5.2 Distribution of patients according to clinical characteristic

5.2.1 Distribution of patients according to past medical history

Table (4-3) showed that 33% of participiants were having +ve past medical history, mainly (48.5%) history of recurrent renal stone.

There are a variety of explanations for high rates of recurrent kidney stones in patients. Some of them may be related to patients' occupations or places of residence with hot climates (that, as previously discussed, enhance the chances of renal stone formation), while others may be associated to lifestyle and dietary habits like (type of food consumption or inadequate water intake (Rajendra, 2020). Additionally, patients with high body mass index have a greater risk of having recurrent kidney stones, as the majority of patients in our study had high BMIs, which may have contributed to the recurrent development of renal stones by the abovementioned mechanism. Medical conditions are additional risk factors for the recurrence of renal stones in patients such as, inherited disorder likes (Hyperuricosuria, hyperoxaluria), hypocitraturia (Rajendra, 2020).

Our result agreed with Bihl and Meyers study (2001), as they found that patients with renal stone have 50% chance of developing recurrent renal stones during their lifetime.

Similar to that, Khan *et al*., (2016), a study which demonstrated that 42.7% of patients with renal stones have a chance of developing renal stones later.

According to our study, 18.2% of patients had hypertension, which is one of the risk factors for kidney stones, Hartman *et al.*, (2015) , analyzed the results of a 24-hour urinalysis in people with high blood pressure with people with normal blood pressure; they revealed that people with high blood pressure excreted less citrate than people with normal blood pressure. Citrate prevents kidney stones from forming, hence a decline in citrate excretion may have contributed to the higher prevalence of kidney stones in hypertension patients.

Also, the study of Rezaee *et al.,* (2017), conclude that there is a significant correlation between renal stone disease and hypertension where 80% of patients with renal stone had history of chronic disease one of them is hypertension.

On other hand, Kohjimoto *et al.*, (2013), in their analysis, which was carried out in the country of Japan in East Asia, revealed that hypertension was an independent risk factor for renal stones, irrespective to sex, age, and other elements of the metabolic syndrome.

The present study revealed that diabetes mellitus type two (insulin resistance) was identified in 12.1% of participants, this is agreed with study of SJ,(2018) , in his study showed that, patients with poor glycemic control have been reported to have increased levels of calcium, oxalate, and uric acid in their urine, which inhibits the elimination of ammonia and citrate and causes urinary acidification, so the probability of developing renal stones is increased by all of these findings .

5.2.2 Distribution of patients according to family history

According to our study table (4.4) showed, 56% of patients had a positive family history of renal stones, previous studies that considered a family history of renal stones as a risk factor are supportive of this finding. The causes of the prevalence of kidney stones in some families may be attributed to a hereditary propensity for the disease, or the family members' similar food and lifestyle habits. Daga *et al.*, (2018), have revealed a strong link between human CaSR gene mutations and hypercalciuria, a condition known to increase the incidence of calcium renal stones.

Unno *et al.*, (2021), in their study, stated that there is a link between kidney stone disease and mitochondrial dysfunction, in patients with a positive maternal family history of stones, maternal inheritance of abnormal mitochondrial DNA may have a role in the early development of stones.

Another similar study is the study of Alblowi *et al*., (2021), in Jedah and Al-Riydh, 56 percent of participants had a positive family history of renal stone disease.

5.2.3 Distribution of patients according to site and radiological features of renal stones of renal stone

In our study, lower pole renal stones affected 60% of the patients, that's agreed with the study of Donaldson *et al*., (2015), which stated that, the most common site for kidney stone is in the lower pole. Also, Almuhanna *et al*., (2018), in their study in, revealed that the lower pole is the most favorable location for renal stones, rather than upper and middle pole.

Similar to the current study, Mourmouris and Skolarikos, (2019) suggested that lower pole kidney stone is the most common in compared with upper and mid pole, due to anatomical factors in addition to gravity. There are many explanation for formation of renal stones in the lower pole of kidney , one of them is unfavorable anatomy of the lower pole delays the flow of urine from the nephron to the ureter, which increases the risk of precipitation of crystals and the development of stones, also there is difficulty of spontaneous passage of small size renal stone related to anatomical characteristic of lower pole.

In the current study, radiopaque renal stones were present in 70% of patients, while 30% were with radiolucent renal stone. Similar to study of, Amir *et al.,* (2018), which done in Saudi Arabia, demonstrated that the most prevalent type of renal stone in the population is calcium oxalate, which supported the current study.

Far away, an international study done in Europe by Skolarikos *et al*., (2015) stated that, the most prevalent form of kidney stone is calcium oxalate, one of the main risk factors for calcium oxalate urolithiasis is hyperoxaluria, and Dietary food is the primary risk factor for hyyperoxaluria (Siener *et al*., 2003).

5.2.4 Distribution of patients according to Blood pressure and pulse rate changes

In our study, as displayed in table (4.7), the p value for diastolic and systolic blood pressure between two periods of assessment was less than 0.001. This indicates that there is significant elevation in the readings of systolic and diastolic blood pressure of patients who had ESWL session.

This result is consisting with that of Huang *et al*., (2017), who found that, there is a risk of blood pressure rising in patients who have ESWL sessions. Also, this study agreed with Canning's study (2018), which stated that, ESWL of the kidney stone was related to a rise in the incidence of hypertension.

Contrarily, findings disagreed with Muhammadamin *et al.*, (2012) study, which carried out in the Iraqi Kirkuk province, revealed that patients who attended an ESWL session did not show any significant increase in blood pressure. While Strohmaier *et al*., (2000), in their study, showed that immediately after ESWL session, systolic blood pressure significantly increases as opposed to diastolic blood pressure, which does not change.

There are several explanation for increase of blood pressure, as will discuss below, there is significant increase in plasma catecholamine level of patients after ESWL session , epinephrine and norepinephrine play a crucial role in controlling blood pressure, by contracting the smooth muscle in the vasculature (via alpha-1 receptors) , and enhanced contractility of cardiac muscle (via beta-1 receptors) that’s lead to increase blood pressure, also dopamine has cardiovascular effects including increase of myocardial contractility and cardiac output, all of these events lead to increase blood pressure (Taylor and Cassagnol, 2021).

Regarding pulse rate , as shown in table (4.8) there was a significant elevation of the pulse rate after session , that's agreed with Skinner and Norman study, (2012), as they revealed that there is significant effect of undergoing ESWL on cardiac heart rate, and they hypothesized that either there is direct mechanical stimulation of the myocardium or a neurohumoral response to treatment or both.

The other possible explanation for increase of pulse rate is due to elevation level of serum catecholamine (as discussed below), as activation of sympathetic nervous system resulting in both positive (inotropic, and chronotropic) effects, also increase level of dopamine may contributed to increase contractility of heart (as dopamine has positive inotropic effect on heart) (Hall, 2021).

5.3 Distribution of patients according to biochemical investigation

5.3.1 Distribution of patients according to Serum blood glucose level

Table (4.9) showed that there were significant variations in the level of serum blood glucose in patients before and after an ESWL session. A previous study conducted by Ahmadi *et al*., (2018), showed that over years, measuring the fasting blood sugars (FBS) of patients had ESWL demonstrated significant increase following session.

An explanation for these differences is that several of the study's participants had previously been diagnosed with diabetes mellitus (as mentioned previously), and many omitted to take their anti-diabetic medicine on the day that they had ESWL sessions. Another explanation is that elevated level of catecholamine may affect the blood glucose of patients. As both epinephrine and norepinephrine modify metabolism by promoting glycogenolysis in the liver (via beta-2 receptors), increasing glucagon secretion (via beta-2 receptors), and decreasing insulin secretion (via alpha-2 receptors) (via beta-3 receptors), resulting an increase blood glucose level (İhsan *et al*., 2021).

5.3.2 Distribution of patients according to serum epinephrine and norepinephrine level

According to tables (4.10) and (4-14) from the current study, there were considerable differences in the serum Epinephrine and Norepinephrine concentration of patients who underwent ESWL session. An old study conducted by Ishihara *et al.,* (1999), demonstrated a significant rise in epinephrine levels in patients receiving ESWL, which is in line with the results of the present study.

Furthermore, Behnia *et al*., (1990), their research from earlier than 30 years ago indicated no noticeable elevation in catecholamine levels in patients who were given ESWL sessions, which is in contrast to the findings of our study.

Unfortunately, there is limited recent study about catecholamines level in patients treated by ESWL.

The most potential explanations for increasing serum catecholamines is direct effects of shock waves on the tissue surrounding the kidneys, including the adrenal medulla, which result in an increase in sympathetic activity and the activation of chromaffin cells that secrete catecholamines (epinephrine and norepinephrine), because of the fact that catecholamine released by medullae can persist in serum for minutes as opposed to catecholamine released by neurons, that does not enter the blood stream. (Paravati and Warrington, 2019).

The other explanation for increasing of catecholamine levels in patients underwent ESWL is indirect effects of adrenal medullae, as having to undergo ESWL sessions for the first time, may be considered as stressful condition and promote the sympathetic fight or flight response resulting in rise of catecholamine level.

Another potential cause of increased catecholamine secretion from the adrenal medullae is the influence of cortisol, which is released from the adrenal cortex during stressful condition and plays a crucial role in stimulating the adrenal medullae to secrete catecholamine (Young *et al*., 2019).

Also, the study reveals that there was no significant correlation between catecholamine level and changing of lithotripter parameters (energy, frequency and number of shock waves).

This may be due to the small sample size of the current study, which may have made the results inconclusive, or it may have been because different patients underwent the parameter changes.

On the other hand, the study stated that there was a significant correlation between stone site and level of serum catecholamine level, as there was more increase in level of epinephrine and norepinephrine in patients whose treated with upper pole renal stones, rather than lower and mid pole. A possible explanation for those changes relating to the location of the adrenal medullae, since it located closely above the kidneys, as additional excitement increased as it approached shock wave streams, sympathetic activity increased, resulting in an increase of releasing catecholamine.

Up to our knowldge, there has been limited research on the correlation between shock wave stream distance and adrenal medullae sympathetic activity.

5.3.3 Distribution of patients according to serum dopamine level: -

As shown in table (4.18), there were significant differences between means of serum dopamine level (pg/ml) pre ESWL and post ESWL. Up to our knowledge, there is not any previous study about the correlation between dopamine level and having an ESWL session, the possible reasons for elevation of dopamine is the anxious condition of patients as having session for the first time.

Also the study showed that there was no correlation between level of dopamine and changes of parameter of lithotripters or site of stone , this may be related to sample size, unfortunately , there was no previous study about relationship between lithotripter's parameter or renal stone site with level of dopamine post session.

6.1 Conclusion

1- Utilizing shock wave lithotripsy to treat kidney stones causes a considerable rise in catecholamine levels (epinephrine, norepinephrine, and dopamine).
2- There is significant association between the site of stone and (epinephrine and norepinephrine) levels following ESWL session, the most considerable elevation of both epinephrine and norepinephrine levels were in patients with upper pole renal stones rather than mid or lower pole.
3- There is no direct effect of lithotripter parameter (frequency, energy, number of shock waves) on level of serum catecholamine in patients underwent ESWL for treatment of renal stone

6.2 Recommendations

1. Further research with larger sample size studying the effect of shockwaves on sympathetic activity of adrenal medullae in patients undergoing ESWL sessions for renal stones.
2. More analysis using different lithotripters is to ascertain whether the effects of shockwaves on the adrenal medullae differ based on the type of lithotripter.
3. Follow up patients who undergo ESWL and investigate any potential long-term effects on the tissue of the adrenal medulla.
4. Increased the ratio of female participants, in the study and examined whether the effect of ESWL on sympathetic activity of adrenal medullae varied according to gender.
5. More research on the impact of ESWL on adrenal tissue in various age groups. Hence, research if aging affects the ESWL of the adrenal medullae.

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