Sudan University of Science and Technology

College of Graduate Studies

Establishment of National Diagnostic Reference Level for bone Radiation Doses in Nuclear Medicine Department in Khartoum – Sudan

تأسيس مستوي تشخيص مرجعي قومي للجرعة الإشعاعية لتصوير العظام بأقسام الطب النووي في السودان- الخرطوم

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of Master degree in Medical Physics

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بسم الله الرحمن الرحيم

قال تعالى :

{وَمَا يَعْلَمُ تَأْوِيلَهُ إِلَّا اللَّهُ وَ
الرَّاسِخُونَ فِي الْعِلْمِ يَقُولُونَ آمَنَّا
بِهِ كُلٌّ مِنْ عِنْدِ رَبِّنَا}

[آل عمران : 7]

Dedication

This thesis dedicate to

My parents

My brothers and sisters

My teachers

ACKNOWLEDGMENT

First I would like to thank Allah and Alhamdulillah, I am heartily thankful to my supervisor Dr. Hussein Ahmed whose encourage, guidance and support me to complete this thesis. Finally, I thank everyone who gave me a bit of Wise and advice.

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List of Abbreviation

IAEA	International Atomic Energy Agency
MDP	methylene diphosphonate
SPECT	Single Photon Emission Computed Tomography
AAPM	American Association of Physics in Medicine
NM	Nuclear Medicine
DNM	Department Nuclear Medicine
PET	Positron Emission Tomography
DRL	Diagnostic Reference Level
ACR	American College of Radiology
QC	Quality Control
ICRP	International Commission of Radiation Protection
NRC	Nuclear Regulation Commission
UK	United Kingdom
EC	European Commission
HDP	Hydroxymethylene diphosphonate
CT	computed tomography

Abstract

A diagnostic reference level (DRL) is an investigational level used to identify unusual high radiation doses in Nuclear Medicine procedures. DRLs are suggested action levels above which a facility should review its methods and determine if acceptable image quality can be achieved at lower doses.

The high specific activity of ^{99m}Tc makes it suitable as a first pass agent, for multiple or sequential studies. Is preferred to ^{99m}Tc - pertechnetate.

A certain amount of radiopharmaceuticals was injected into each patient and was immediately imaged with gamma camera to calculate the activity through the conjugated view method.

According to the American Association of Physics in Medicine (AAPM) recommendation that the radiation dose for bone scan (^{99m}Tc –MDP) should be between 555 MBq (15 mCi) and 970 MBq (26 mCi) , this study showed that the patients received a radiation dose less than 26 mCi with acceptable image quality.

Therefore this study can be considered as a basis for the establishment of dose reference level activity for bone scan of nuclear medicine departments in Sudan.

ملخص البحث

مستوى التشخيص المرجعي هو مستوى التحقيق المستخدم لتحديد جرعات الإشعاع العالية او الغير عادية في إجراءات الطب النووي. وتعتبر وحدات مستوى التشخيص المرجعي مستويات عمل مقترحة يجب أن تراجع طرقه وتحدد ما إذا كان يمكن تحقيق جودة الصورة المقبولة عند الجرعات المنخفضة.

النشاط الاشعاعي العالي لل ^{99m}Tc يجعله مناسب كخيار أولى لدراسات متعددة في الطب النووي. ويفضل ^{99m}Tc - بيرتشنيتات.

تم حقن كمية معينة من المستحضرات الصيدلانية الإشعاعية في كل مريض وتم تصويره بجهاز الغاما كاميرا ثنائي لرأس لحساب النشاط الاشعاعي بجسم المريض.

وفقا لتوصية الرابطة الأمريكية للفيزياء الطبية فأن الجرعة الإشعاعية لفحص العظام ينبغي أن تكون بين 555 MBq (15 mCi) و 970 MBq (26 mCi) ، وأظهرت هذه الدراسة أن المرضى تلقوا جرعة إشعاعية أقل من 26 mCi مع جودة مقبولة للصورة.

لذلك يمكن اعتبار هذه الدراسة أساسا لإنشاء نشاط مستوى مرجعي للجرعات لفحص العظام بأقسام الطب النووي في السودان.

Chapter One

Introduction

CHAPTER ONE

1.1 Introduction:

Nuclear medicine is a medical specialty involving the application of radioactive substances in the diagnosis and treatment of disease. Nuclear medicine, in a sense, is "radiology done inside out" because it records radiation emitting from within the body rather than radiation that is generated by external sources like X-rays. In addition, nuclear medicine scans differ from radiology as the emphasis is not on imaging anatomy but the function and for such reason, it is called a physiological imaging modality. Single Photon Emission Computed Tomography or SPECT and Positron Emission Tomography or PET scans are the two most common imaging modalities in nuclear medicine. (Henkin, 1996)

Nuclear medicine examinations provide unique information including details on both function and anatomic structure of the body, For many diseases scans yield the most useful information needed to make a diagnosis or to determine appropriate treatment, is less expensive and may yield more precise information than exploratory surgery, and its offers the potential to identify disease in its earliest stage, often before symptoms occur or abnormalities can be detected with other diagnostic tests. (Wall, 2004)

The ICRP introduced the term diagnostic reference levels (also known as guidance levels) in 1996. In the case of nuclear medicine the quantity of reference is generally taken to be the radiopharmaceutical activity administered to "a typical adult patient". Reference levels are usually set at the 75th percentile (3rd quartile) or within a specified range of the median (2nd quartile) of the values used in routine clinical practice, parameters which are independent of the shape of the distribution of values or the presence of outlying values. The ICRP recommends

that reference levels should be established by the appropriate professional organizations, and the regulatory organizations that legalized use of DRL, including the ICRP, American College of Radiology (ACR), American Association of Physicists in Medicine (AAPM), United Kingdom (U.K.) Health Protection Agency, International Atomic Energy Agency (IAEA), and European Commission (EC). Also the ICRP recommends the establishment of diagnostic reference levels as a tool for optimizing the radiation dose delivered to patients in the course of diagnostic and/or therapeutic procedures. (Johnson. et al, 2000)

Definition of Diagnostic Reference Level (DRL): Is defined by the International Commission on Radiological Protection (ICRP) as;

"A form of investigation level, applied to an easily measured quantity, usually the absorbed dose in air, or tissue-equivalent material at the surface of a simple phantom or a representative patient." (ICRP1996).

Also it is defined by the Council of the European Union as; "Dose levels in medical radiodiagnostic practices or, in the case of radio-pharmaceuticals, levels of activity, for typical examinations for groups of standard-sized patients or standard phantoms for broadly defined types of equipment. These levels are expected not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied" (European Commission: Luxemburg, 1997)

Diagnostic reference levels are used as investigation levels, they are advisory and NOT a dose limit, therefore should not be applied to individual patients, assess the dose impact of the introduction of new protocols, for international comparative dosimetry, as a tool for optimizing the radiation dose delivered to patients, to help avoid excessive radiation dose to the patient that does not contribute additional clinical information

value to the medical imaging task, and Provide compliance with the relevant state and territory regulatory requirements. (Arpansa rps 14, 2008) (IAEA, 200)

It should be noted that these effective dose conversions are to be used with caution. They should not be applied to an individual but rather are statistical estimates of a dose and risk to a population who may receive that dose. (Sam 2008).

1.2 problem of study:

The increasing of the activity in the nuclear medicine cause increasing of patient dose, the activity of radio nuclide affect by the patient properties, there must be a local stander in nuclear medicine centers.

1.3 Objectives of Study:

1.3.1 General objective:

To establish National Diagnostic Reference Level for bone scan dose in nuclear medicine practice and to avoid excessive radiation dose to the patient that does not contribute additional clinical information value to the medical imaging task at canter A and canter B Nuclear Medicine Department in Sudan.

1.3.2 Specific objectives:

- To establish National Diagnostic Reference Level for bone scan dose in nuclear medicine practice at canter A.
- To establish National Diagnostic Reference Level for bone scan dose in nuclear medicine practice at canter B.

- To compare between DRLs for the tow center and with International DRL.
- To major the bone Dose in nuclear medicine department.
- To investigate for bone Dose in the two centers Nuclear Medicine Examinations.

1.4 thesis outline:

The following thesis will be sketched in five chapters. Chapter one will highlight the introduction, problem of the study, objectives and thesis outlines. Chapter two will deal with literature review. Chapter three will shows the methodology. Chapter four will presents the results. Chapter five will imply the discussion, conclusion and recommendation

Chapter Two
Theoretical Background and Literature Review

CHAPTER TOW

Theoretical Background:

2.1 Skeleton Anatomy and Physiology:

The skeletal system or the bone serves as a framework to support the soft tissues of the body. It is consists of cells, fibers, and matrix. It is hard because of the calcification of its extracellular matrix and possesses a degree of elasticity because of the presence of organic fibers. It is a live functional tissue undergoing continuous metabolic changes. It serves as a storehouse for calcium and phosphorus, protects soft organs, and works as a lever for muscles. Bone tissues consist of organic and inorganic constituents, the organic matrix accounting for almost one third of the weight of the bone, and the inorganic matrix forming the rest. The inorganic matrix is called hydroxyapatite crystal and is primarily composed of calcium phosphate and, to a small extent, carbonate and hydroxide. Inorganic calcium salts deposit within the frame of the organic matrix and give strong rigidity to the bone. The blood supply is essential for the growth of new bone; a continuous exchange of minerals takes place between bone and plasma, and the minerals are used in now bone formation. This process of mineral exchange and new bone formation, by which new bone gradually replaces old bone, is called bone accretion. (Richard S. Snell, 2007)

Bone metastasis of cancers occurs commonly when tumor cells move into the bone marrow compartment present in the axial skeleton. With continuous growth of the tumor, the surrounding bone tissues undergo osteoblastic transformation indicating the metastatic process. Bone imaging is ideal in accurately demonstrating the metastases of different cancers in bone and also monitoring the response of cancers to therapy. . (Ellis, Harold et. 2005)

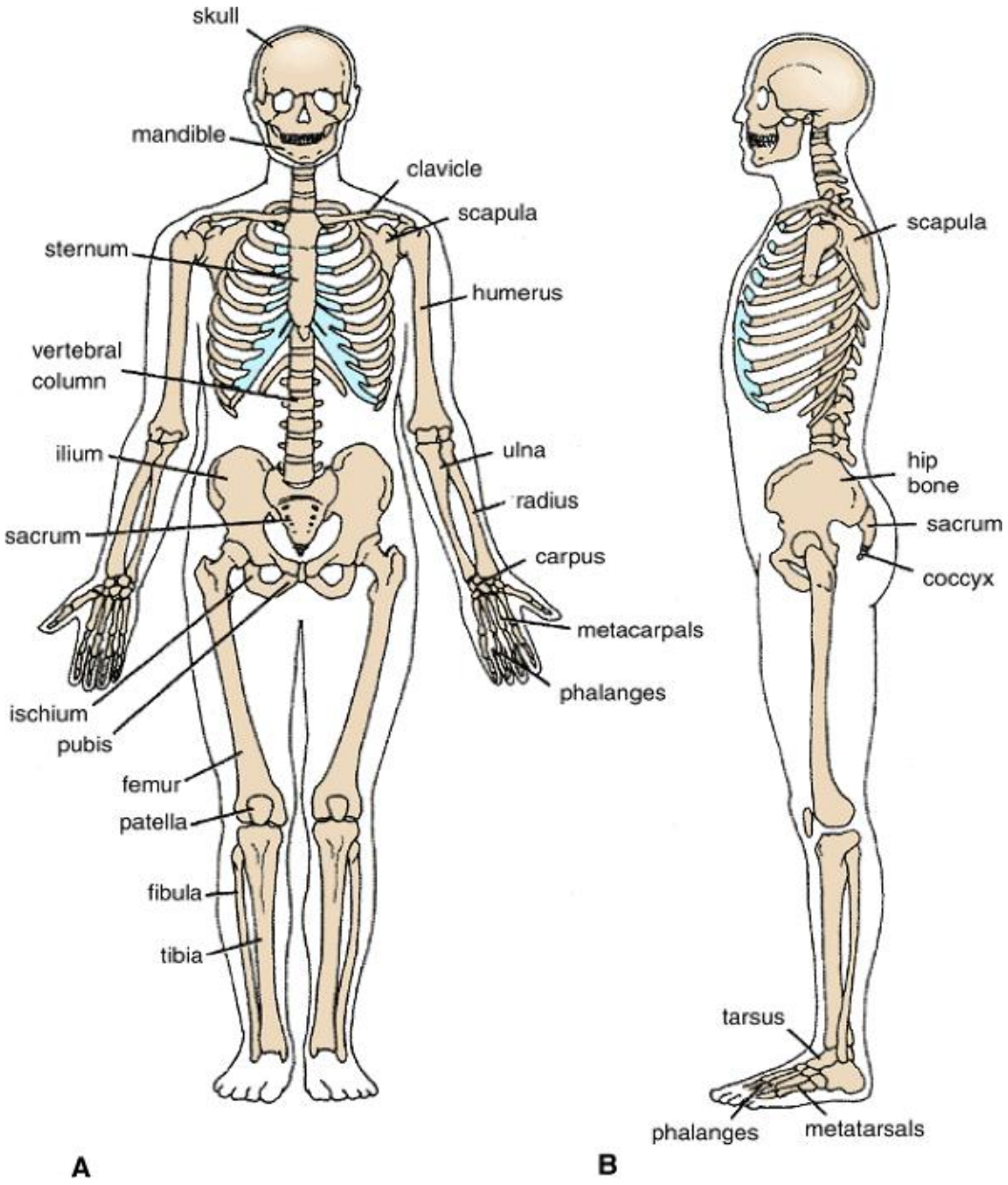


FIGURE 2.1 Human skeleton: Bone exists in two forms: compact and cancellous. Compact bone appears as a solid mass; cancellous bone consists of a branching network of trabeculae. The trabeculae are arranged in such a manner as to resist the stresses and strains to which the bone is exposed. (Richard S. Snell, 2007)

2.2 Radiopharmaceuticals and Imaging Techniques:

The rationale for using phosphonate compounds for bone scanning lies in the composition of the bone matrix containing calcium phosphate that can be exchanged with phosphonate compounds. Two compounds, ^{99m}Tc -MDP and ^{99m}Tc HDP, are commercially available for bone imaging, of which ^{99m}Tc –MDP is most commonly used. Following IV administration, ^{99m}Tc -MDP is cleared from the plasma with a half-time of 3–4 min. About 10% of the injected dosage remains in the blood at 1 h post-injection and less than 1% at 24 h. Urinary excretion is 50% and the remaining 50% is retained by the skeleton in 24 h. Approximately 10–20 mCi (370–740 MBq) ^{99m}Tc -MDP or ^{99m}Tc -HDP is injected intravenously and scanning is performed with the patient supine 2–3 h after injection. The 2- to 3-h waiting period is needed to reduce the background against the bone, and the patient is asked to void before imaging so that the bladder activity does not blur the pelvic region on the image. Whole-body scanning is performed by moving the detector from head to toe of the patient using either a single-head or a dual-head camera equipped with Skeleton 297 a low-energy, all-purpose parallel hole collimator. Static spot images are obtained with a single-head camera, whereas both anterior and posterior scans are obtained simultaneously using a dual-head whole-body camera.To distinguish between cellulitis and osteomyelitis in the distal extremities, three-phase bone images (flow, blood pool, and bone uptake) are obtained by giving a bolus injection of 30 mCi (1.11 GBq) 99mTc-MDP. In the flow phase,images are obtained every 2 s for 60 s, followed by blood pool imaging immediately and bone uptake imaging at 3–5 h after injection. Due to hyperemia incellulitis, the tracer localizes in both the flow and blood pool phases, butdisappears in the delayed bone uptake phase. On the other hand, in osteomyelitis, wherein some associated hyperemia exists, the tracer uptake is seen in theflow and blood pool phases, with a further increase in localization in the

boneuptake phase. In some cases, the background clearance is not optimum becauseof vascular insufficiency; a fourth phase bone image may be required, which is usually performed the next day to delineate bone uptake better. Regional bone blood flowrate, bone formation rate, and extraction efficiency are the major factors that influence the bone uptake of phosphonate complexes. Ingeneral, the higher the rates of blood flow and bone formation, the greater the bone uptake of radiotracer. There are two hypotheses on the bone uptake mechanism of phosphonate compounds: hydroxyapatite uptake and collagen uptake. In the hydroxyapatite uptake theory, it has been suggested that hydroxyapatite crystal removes the phosphonate component successfully from 99mTc-phosphate complexes, thus setting the reduced technetium free to bind independently to hydroxyapatite at another binding site. In the collagen uptake theory, it has been suggested that ^{99m}Tc -phosphonate complexes localize in both inorganic and organic matrices of bone, the latter uptake depending on the amount of immature collagen present. It has also been found that ^{99m}Tc phosphonate complexes localize in soft tissues and tumors to a variable degree. (G.B. Saha, 2010)

2.3 Bone Imaging agents:

The most relevant bone imaging agents can be classified into three different chemical structures:

- Inorganic phosphates that have phosphorous –oxygen bonds, e.g. pyrophosphate and polyphosphates.
- Organic phosphonates that have strong phosphorous – carbon bonds, e.g. MDP, medronic acid, HMDP, oxidronic acid and HEDP (1-hydroxylethylidene-1, 1 –diphosphonate) – Etidronic acid.
- Imidodiphosphonates :

^{99m}Tc –labeled diphosphonates are used for diagnostic bone scintigraphy. Application is especially recommended in case of primary bone tumor and bone metastases of other tumors (e.g. prostate, breast and lung cancers). The required dose for an adult patient (70 Kg) is 370 – 470 MBq at the time of application. The labeling should be carried out within 3 – 6 GBq pertechnetate activity.

After administration, ^{99m}Tc – MDP, ^{99m}Tc –HMDP, ^{99m}Tc –HEDP and others, leaves the blood and concentrates in the skeleton and, to a negligible extent, to soft tissues. A much smaller quantity of injected ^{99m}Tc -Diphosphonates binds to the blood plasma proteins, which results in a very slight body background. The fraction unbound to the skeleton washes out from the body in the urine. In patients, approximately half of the injected activity binds to the skeleton . (Gopal B. Saha, 2003)

2.4 ^{99m}Tc-^{99}Mo Generator:

A generator is constructed on the principle of the decay growth relationship between a long-lived parent radionuclide and its short-lived daughter radionuclide. The chemical property of the daughter nuclide must be distinctly different from that of the parent nuclide so that the former can be readily separated. In a generator, basically a long-lived parent nuclide is allowed to decay to its short-lived daughter nuclide and the latter is then chemically separated. The importance of radionuclide generators lies in the fact that they are easily transportable and serve as sources of short lived radionuclides in institutions far from the site of a cyclotron or reactor facility. (Guillaume et al. 1986)

The dry column generator was developed to alleviate poor elution yields of ^{99m}TcO4 by removing saline after elution. This decreases the amount of radiolysis products formed. The dry column generator employs a 5-20 ml saline charge, which is applied to au exterior part of the generator. An evacuated vial draws saline through the generator to remove ^{99m}TcO4, followed by air to dry the column

caving the air on the column promotes oxidation of any reduced ^{99m}Tc species back to + 7 valence state of ^{99m}TcO4 which can then be eluted (Antoni and Langstrom, 2005).

Positron emitters such as 11C, 18N, and 15O can be substituted for stable atoms of the same elements in compounds of biologic importance. This results in radiolabeled compounds with exactly the same biochemical properties as the original compound. Alternatively, 18F, another positron-emitting radionuclide, can be substituted for hydrogen to produce labeled analogs. Several hundreds of compounds have been synthesized with 11C, 18N, 18O, or 18F labels for imaging with positron emission tomography (PET). The short half-life of 11C, 18N, 18O, or 18F, and requires in-house radionuclide production in a biomedical cyclotron and rapid synthesis techniques to incorporate them with radiopharmaceuticals. On the other hand, the relatively longer half-life of 18F permits its distribution within a radius of a few hundred miles from the site of production, thus obviating the need of a cyclotron in the nuclear medicine imaging facility (Bailey et al. 2005).

2.5 Elution of the ^{99}Mo → ^{99m}Tc generator:

The procedures for elution are designed to provide a sterile, pyrogen free product suitable for human injection or for elaboration into other radiopharmaceutical preparations. Commercial generators will be prepared from sterilized and medically suitable components and with proper care can be maintained in this state through their working life. Because the design of individual commercial generators varies, the precise methods used for their elution will also vary, however, the same general principles apply to all designs. (Alrabiah et al .1996)

The generator will be removed from its shipping container and placed in an appropriate area in the laboratory. In some cases an auxiliary shield will be used to reduce operator radiation dose during the dispensing procedures.

A sterile isotonic saline solution must be provided for the elution step. In most designs the eluent will be obtained from a standard septum vial by attaching the vial to the generator using the inlet spike provided for this purpose. In this latter design there will be a set procedure to maintain sterility of the system, which will involve wiping the elution vial with an alcohol swab and allowing it to dry, then uncovering the inlet spike on the generator and attaching the vial by piercing the spike into the vial. In some generator designs the saline is provided in the form of an internal reservoir with sufficient volume to provide all the elutions that will be performed during the lifetime of the generator. (Gopal B. Saha, 2003)

A sterile elution vial of sufficient volume to hold the eluate to be drawn through the generator is prepared. These vials have been evacuated and this vacuum will serve to draw the saline through the generator. The eluate vial is placed in a suitable shield to absorb the radiation from the ^{99m}Tc activity that will be removed from the generator. The septum is wiped with an alcohol swab and allowed to dry. Removing a protective cap exposes the elution port and generally a fresh sterile needle is placed on the elution port for this and each subsequent elution. The elution vial in its shield is then pushed down onto the elution needle fully piercing the septum. The vacuum in the elution vial causes the saline to be drawn through the generator column thereby eluting the ^{99m}Tc activity. This step may take a few minutes as the saline moves through the bed of alumina and is pulled through the internal plumbing of the generator. The volume of eluted radioactivity is controlled by the size of the evacuated vial used and/or by the supply of isotonic saline solution provided in the vial attached to the inlet spike. Various generator designs provide supports and mechanical devices to aid in the alignment and spiking of the inlet and elution vials.

The elution vial in its shield is removed from the generator and the elution needle can be capped or protected or replaced with a fresh sterile needle. If the generator

uses an eluent vial this will be left on the inlet needle until the next elution. The elution vial shields are usually equipped with a shielded cover that protects against radiation passing through the exposed septum end of the vial. The vial is taken for activity assay and quality control tests of the eluted ^{99m}Tc before being released for dispensing or use in the preparation of various ^{99m}Tc radio-pharmaceuticals. Various methods are used for appropriate labelling and inventory control of this product. Adequate radiation shielding must be maintained at all times.

Subsequent elutions follow the same general set of steps as outlined above. Depending on the generator design it may be necessary to replace the used eluent vial from the previous elution with a new supply of sterile isotonic saline in a fresh vial. The elution port should be exposed and provided with a fresh sterile needle if this was not done as part of the previous elution protocol. All remaining steps in the elution will remain the same as with the first elution. (IAEA.2016)

2.6 Properties of technetium – 99m:

Technetium – 99m has suitable physical half- life of six hours, which is similar to the time from preparation to injection. If the half – life is too short, much more activity must be prepared than is actually injected. It's half – life is sufficiently long so that needed medical information can be obtained, yet short enough to minimize radiation dose to the patient.(Ramesh Chandra, 2001; Penelope Allisy et al. 2008).

It emits mono energetic gamma rays of 140 Kev , high enough to well penetrate the tissues and low enough for efficient detection .This is because it is close to optimum for a NaI (Tl) crystal (150-200 Kev) of the gamma camera, It decays to a radionuclide of a very long half- life i.e99Tc (2.1X105),It has a high specific activity (high activity per unit volume) and easily and firmly attached to a number of pharmaceuticals without affecting the metabolism thereof (Penelope Allisy et al 2008).

Readily available at the hospital site in a generator system, a reasonable cost, available in a sterile, pyrogens -free, and carrier - Free State from 99Mo –99mTc generators (Gopal B. Saha, 1998).

Chemically technetium is a silvery – grey metal that tarnishes slowly in moist air, and it belongs to group V11B (Mn, Tc and Re). It can exist in eight oxidation states, namely, 1- to 7+, and the common oxidation states of these are+7, +5 and +4. When it is obtained from a generator in normal saline (0.9% Nacl) as pertechnetate ion (^{99m}TcO4), technetium is in the +7 valence state, which is the most stable of all valence states of technetium in aqueous solutions. Technetium forms both soluble and insoluble compounds. With the exception of pertechnetate and 99mTc – sulfur colloid, all other radiopharmaceuticals containing technetium are in an oxidation state lower than seven. Therefore, technetium needs to be reduced to a lower oxidation state before it can be utilized in a variety of useful ligands such as DTPA.(Gobal B. Saha; David H. et al 2ooo; Paul Christian et al 2004; Sam A.K.2008).

The reduction process is very important since the pertechnetate ion is a mild oxidizing agent and, chemically, a rather non-reactive species which does not label any compound by direct addition (17, 20). Various reducing agents that have been used are stannous chloride (Sncl2. 2H2 o), stannous citrate, stannous tartrate, concentrated Hcl, sodium borohydride (Na BH4), dithionite and ferrous sulfate. Among these, stannous chloride is the most commonly used reducing agent in most preparations of ^{99m}Tc – labeled compounds (Gobal B. Saha 1998; Paul E. Christian 2004).

Another method of reduction of ^{99m}Tc from +7 oxidation state to a lower oxidation state involves the electrolysis of a mixture of sodium pertechnetate and the compound to be labeled using an anode of zirconium. The amount of ^{99m}Tc atoms in the ^{99m}Tc eluate is very small, and therefore only a minimal amount of Sn2+ is

required for reduction of such a small quantity of ^{99m}Tc. However, enough Sn2+is added to ensure complete reduction. The ratio of Sn2+ ions to 99mTc atoms may be as large as106 (Gopal B. Saha 1998).

The reduced ^{99m}Tc species are chemically reactive and combine with a wide variety of chelating agents. A schematic reaction would be: Reduced ^{99m}Tc + chelating agent ^{99m}Tc – chelate. In a typical preparation of ^{99m}Tc – radiopharmaceuticals in the kit, the quantity of free pertechnetate usually remains within the acceptable limit. However, the presence of oxygen in the vial, particularly before the oxidation of 99mTc, can cause oxidation of the stannous ion to stannic ion whereby the amount of stannous ion available for reduction of Tc7+ decreases. This results in an increase in free ^{99m}TcO4 in ^{99m}Tc - radiopharmaceuticals. Further, the high activity of ^{99m}Tc in the presence of oxygen can cause radiolysis of water or other products in the sample, producing hydroxyl (OH.), alkoxy (RO.) and proxy (RO2.) free radicals. These species interact with ^{99m}Tc – chelates producing free ^{99m}TcO4 in the sample .However, limits of ^{99m}Tc activitysuggested for adding to the commercial kits are sufficiently low such that the radiolytic affects are normally negligible. The above effects can be mitigated by using sufficient quantity of stannous ion and by avoiding oxygen, air, or any oxidizing agent in the vial throughout its shelf life. In some kits such as MDP kits, antioxidants (e.g. ascorbic acid and gentisic acid) are added to prevent oxidation (Gopal B. Saha 1998).

After the reduction of ^{99m}Tc, it may undergo hydrolysis when it is reduced in an aqueous medium in the absence of any complexion agent. In this case, reduced ^{99m}Tc reacts with water to form various hydrolyzed species, depending on the PH, duration of hydrolysis and presence of other agent's .The analysis of chemical reactions shows that hydrolyzed technetium is a compound of 99mTc O4complexed with other ingredients (e.g. .SnO, MoO3 or Al). This hydrolysis

competes with the chelation process of the desired compound and thus reduces the yield of ^{99m}Tc - chelate. The hydrolyzed species can also interfere with the diagnostic test in question if they are present in large quantities in the radiopharmaceutical (Roy P. Parker et al 1984; Gopal B. Saha 1998).

The hydrolytic reaction may also occur to some extent even in the presence of commixing agent, and the presence of hydrolyzed99mTc species in a radiopharmaceutical preparation may be missed unless the analytical procedures are well chosen (Roy P. Parker et al 1984).

The use of stannous chloride has a disadvantage in that the Sn2+ ion also readily undergoes hydrolysis in aqueous solution at PH 6 to 7, and forms insoluble colloids. These colloids bind to reduced ^{99m}Tc and thus compromise the labeling yield. For this reason, an acid is added to prevent the hydrolysis of Sn2+ before the reduction of technetium if the preparation is made using basicingredients rather than a kit (Gopal B. Saha 1998).

These two disadvantages, namely the hydrolysis of reduced ^{99m}Tc and Sn2+, can be circumvented by adding enough chelating agents. The latter will bind to reduced ^{99m}Tc and Sn2+, and thus prevent their hydrolysis. The ratio of the chelating agent to Sn2+ should be large enough to ensure complete binding. Binding between the chelating agent and reduced ^{99m}Tc or Sn2+ is highly dependent on the affinity constant of the chelating agent. If it is a weak chelating agent (e.g. phosphate compounds), then hydrolyzed species in the ^{99m}Tc – labeled preparation tend to be relatively high. However, if the chelating agent has a high- affinity constant (e.g. DTPA) then the amount of hydrolyzed species will be minimal (Gopal B. Saha 1998).

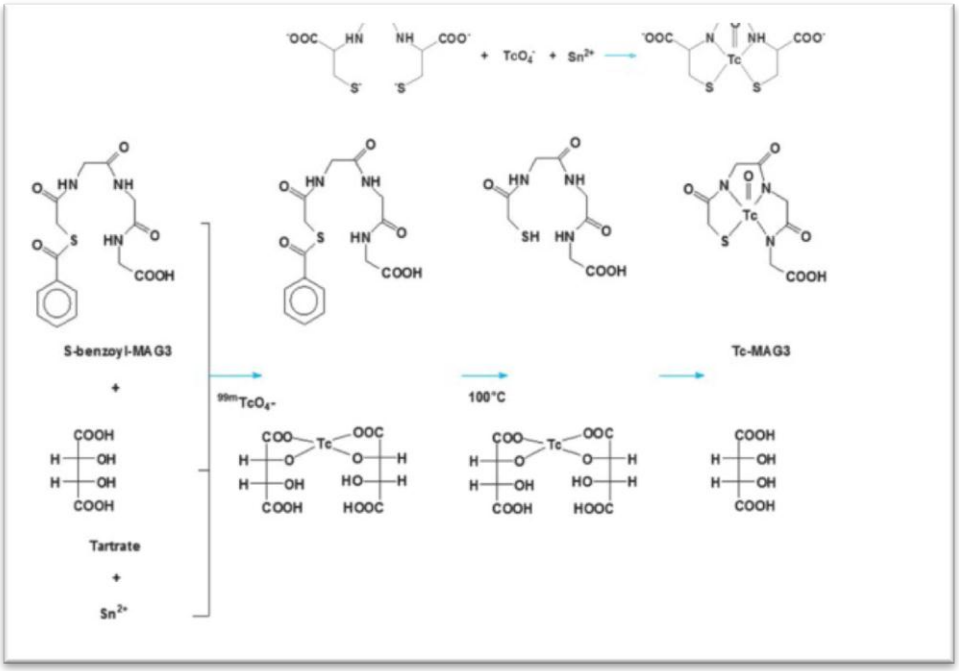


Figure2.2. Direct labeling can be performed if ligand is present in metal bindingform (Antoni and Langstrom, 2005).

2.7 Technetium 99m-Labeled Radiopharmaceuticals:

The ^{99}Mo/^{99m}Tc generator produces technetium in the form of ^{99m}TcO4. A number of "cold kits" are available that allow different ^{99m}Tc complexes to be produced by simply mixing the ^{99m}TcO4 and the contents of the cold kit together. The cold kit generally contains a reducing agent, usually stannous chloride, which reduces the ^{99m}Tc to lower oxidation states, allowing it to bind to a complexion agent (also known as the legend) to form the radiopharmaceutical. Using these kits, a range of ^{99m}Tc labe1ed radiopharmaceuticals that are targeted to different organ systems and different biologic processes can be prepared quickly and conveniently in the hospital setting.

2.8 Laboratory techniques:

Correct handling of radiopharmaceuticals ensures good aseptic techniques. All procedures in the hot laboratory are designed to optimize patient care and minimize radiation exposure to all personnel in the department. The patient must receive the correct radiopharmaceiitica1 at the correct dose with high radiochemical purity. This requires that accurate and sterile doses are prepared for patient administration by well trained and qualified personnel.

Aseptic techniques and sterile and pyrogen – free ingredients are used at all times to minimize bacterial and pyrogen contamination. Appropriate records must he maintained to document the receipt, patient use, and ultimate disposition of all radioactive materials. To minimize the chance of errors, be sure the work area is clear. Work with only one radiopharmaceutical agent at a time. In addition, check the dose calibrator setting when assaying the patient's dose (Alrabiah et al. 1996).

2.9 Quality control tests of radiopharmaceuticals:

Quality control in radiopharmaceutical preparation is important to protect the patient and to ensure that the radiopharmaceutical localizes in the intended area. As with any parenteral substance, radiopharmaceuticals must be sterile and free of pyrogens and chemical, radiochemical, or radionuclidic impurities. Throughout the preparation process, Q.C of radiopharmaceuticals is primarily performed on ^{99m}Tc – radiopharmaceuticals. The first step in Q.C. is to ensure that the radionuclide is pure (Fred A. Mettler 2006).

Quality control tests must be performed after the final step of preparation of the radiopharmaceutical. The quality control tests associated with the kits formulation and production of radionuclides from primary sources are performed by manufacturers, while those associated with the final step of the preparation of the

radiopharmaceutical are performed in the radiopharmacy. When a labeled compound is prepared for use in human body or in animaltests, extremely high standards of purity have to be maintained. The QC of radiopharmaceuticals before use when prepared in-house is of paramount importance as it serves to assure that the person preparing the radiopharmaceuticals has not made some blunder in carrying out the instructions of preparing the generators and the kits . The QC also permits the preparer to assure that the used kit gives the tagging .In addition , it provides information about whether the preparation can be successful in situations in which following the exact instructions was not feasible or was not what the preparer deemed best for the current situation (Sam,2008 , Sam and Derar 2009).

2.9.1 Molybdenum breakthrough test:

This is one of the so-called radionuclidic purity tests; the other is Aluminum breakthrough test. Radionuclidic purity is defined as: the proportion of the stated radionuclide that is present in the stated chemical form (18 N.M Khalid,2011).
^{99}Mo activity is likely to be eluted in trace quantities along with ^{99m}Tc activity.
This is called the ^{99}Mo or Moly breakthrough. The presence of ^{99}Mo gives unnecessary radiation dose to the patient. According to the Nuclear Regulatory Commission (NRC) regulations, the acceptable limit for ^{99}Mo breakthrough is 0.15 μCi (5.5 KBq) per millicurie (37 MBq) of ^{99m}Tc at the time of injection. As a rule, if the ratio is less than 0.038 at time of elution, the material will be suitable for injection for at least 12 hours . ^{99}Mo breakthrough is determined by the detection of high energy photons (740 Kev – 780 Kev)of ^{99}Mo in a dose calibrator after stopping the 140 Kev photons of 99mTc in a lead container (6mm thick). The above mentioned limit is obtained by dividing the activity (μCi) of ^{99}Mo by the activity (mCi) of ^{99m}Tc (Gobal B Saha 2001 , Sam A. K ,2008) .

It is well known that 4 mm of lead shielding reduces the ^{99m}Tc radiation by a factor of 5x 104 , whereas the ^{99}Mo radiation is reduced by a factor of 2 (Fred A. Mettler 2006 ,Sam A. K ,2008).

The test procedure can be done as follows:-

- Place the empty lead shield in the dose calibrator and zero the calibrator.
- Place the eluate in the lead shield and record the activity reading using the ^{99}Mo assay dial setting.
- Remove the lead and record the activity at the 99mTc setting.
- Determine the activity ratio by dividing the ^{99}Mo activity by the ^{99m}Tc activity, which should be less than 0.15 μCi ^{99}Mo per mCi ^{99m}Tc, and less than 5 μCi per dose given to the patient, as mentioned before. Deviation of ^{99}Mo activity may be due to the lead container not fulfilling the measurement requirements, so the lead shielding used must be of homogeneous quality and contains no holes in the casting. The presence of holes will allow part of the ^{99m}Tc activity to contribute to the ^{99}Mo measurements and results in high ^{99}Mo values .For any patient injected with larger amounts of ^{99}Mo, testing of the generator eluate for the presence of this radionuclide impurity is mandatory (Sam, 2008).

2.9.2 Aluminum ion breakthrough test:

Contamination of eluates with alumina from column chromatographic generators has been a source of considerable concern. Labeling procedures can be adversely affected by small quantities of aluminum compounds, and this contamination should be monitored often (Buck A. Rhodes, 1977).

Soluble "aluminum ion breakthrough" can, under certain conditions, appear in

the eluate. While not harmful to the patient, it interferes with preparation of ^{99m}Tc -RBC labeling, ^{99m}Tc -bone agents and ^{99m}Tc -sulfer colloid and thus causes degradation in image quality due to poor incorporation of ^{99m}Tc into the carrier. Very large colloid particles (sulfur colloids) , which may be produced during preparation of ^{99m}Tc – SC , due to high levels of aluminum ions in the eluate , may result in increased lung uptake at the expense of liver uptake. It is therefore, mandatory to check every eluate of ^{99m}Tc generator for aluminum ion impurity and to prove that the level of this chemical impurity does not exceed 10μg Al3+per ml of eluate which is recommended as an acceptable limit (James H. Thrall, 2001, Sam, 2008).

The test kit that measures Al3+ ion is a special colorimetric test paper strip containing a chemical sensitive to the presence of aluminum ion at the microgram level. The test is performed by placing a drop of the eluate on one end of the test paper, a drop of a standard solution of Al3+, with concentration of 10 ppm, is placed on the other end of the test strip. If the color at the center of the drop of eluate is less red than that of the standard solution, the eluate has passed the aluminum breakthrough test, i.e. the eluate contains less than 10 μg/ ml of Al3+, which is the limit set out by the USP, and lies within the BP and EP limit of 20μg/ml. The test may be carried out on the remains of the first eluate from each generator (Sam 2008, P.F.Sharp1989).

Previous studies:

Fatemeh Niksirat, Ali Shabestani Monfared et al , 2016 Based on the data of this study, the collective effective dose was 95.628 manSv, leading to a mean effective dose of 0.03 mSv per capita. It was also observed that the myocardial perfusion was the most common procedure (50%). The 75th percentile of the distribution of

administered activity (AA) represents the DRL. The AAA and the 75th percentile of the distribution of AA are slightly higher than DRL of most European countries.

Niksiratet al, Jan 2016:

This study conducted a review on nuclear medicine (NM) services in Mazandaran Province With a view to establish adult diagnostic reference levels (DRLs) and provides updated data on population radiation exposure resulting from diagnostic NM procedures. The data were collected from all censers in all cities of Mazandaran Province in the North of Iran from March 2014 to February 2015. The 75th percentile of the distribution and the average administered activity (AAA) were calculated and the average effective dose per examination, collective effective dose to the population and annual effective dose per capita were estimated using dose conversion factors. The gathered data were analyzed via SPSS (version 18) software using descriptive statistics. Based on the data of this study, the collective effective dose was 95.628 mSv, leading to a mean effective dose of 0.03 mSv per capita. It was also observed that the myocardial perfusion was the most common procedure (50%). The 75th percentile of the distribution of administered activity (AA) represents the DRL. The AAA and the 75th percentile of the distribution of AA are slightly higher than DRL of most European countries. Myocardial perfusion is responsible for most of the collective effective dose and it is better to establish national DRLs for myocardial perfusion and review some DRL values through the participation of NM specialists in the future. Keywords: Collective effective dose, diagnostic reference levels, nuclear medicine, radiation exposure.

Jose willegaignon et al, 2015 :

a total of 107 NMSs in brazil agreed to participate in the project. from the 64 nuclear medicine procedure studied bone kidney and parathyroid scan were found

to be used in more than 85%of all the NMSs there was a large disparity among the activities administration when applying the same procedure this reaching in some cases more than 20time between the lowest and the highest .diagnostic exam based ^{67}Ga ,^{201}TI , ^{131}I radioisotopes proved to be the major exam administering radiation doses to patient . On introducing the DRL concept into clinical routine the minimum reduction in radiation doses received .

GökçeKaanAtaç et al, 2015:

They aimed to establish the first diagnostic reference levels (DRLs) for computed tomography (CT) examinations in adult and paediatric patients in Turkey and compare these with international DRLs. CT performance information and examination parameters (for head, chest, high-resolution CT of the chest [HRCT-chest], abdominal, and pelvic protocols) from 1607 hospitals were collected via survey. Dose length products and effective doses for standard patient sizes were calculated from the reported volume CT dose index (CTDIvol). The median number of protocols reported from the 167 responding hospitals (10% response rate) was 102 across five different age groups. Third quartile CTDI values for adult pelvic and all paediatric body protocols were higher than the European Commission standards but were comparable to studies conducted in other countries vole. The radiation dose indicators for adult patients were similar to those reported in the literature, except for those associated with head protocols. CT protocol optimization is necessary for adult head and paediatric chest, HRCT-chest, abdominal, and pelvic protocols. The findings from this study are recommended for use as national DRLs in Turkey.

Chapter Three
Materials and Methods

CHAPTER THREE

Material and method

3.1. Materials of the study:

The following study is an experimental study designed and conducted in Center A & Center B which are located in Khartoum. The QC tests in this work were conducted in accordance with the internationally accepted standards for dose calibrators. The tests included constancy (reproducibility), accuracy, precision, background, linearity, clock accuracy and geometry

3.1.1. Dose Calibrator:

The nuclear medicine department of Elnilein medical diagnostic center uses dose calibrator model CAPINTEC CII CRCR-25R, manufactured on July 2008. The ionization chamber is a thin wall, deep well, high pressure type 13.6 Kg weight, with dimensions of 25 cm high×6 cm diameter and interconnecting cable of 3.7m. The resolution of 0.01 MBq (0.01 μCi) maximum. Response time is within 2 seconds, for very low activity sample 4-16 seconds.

3.1.2 ^{99m}Tc:

The dose calibrator was tested in place without any movement, and with some modifications to the quality control procedures according to the dose calibrator type and manufacturers recommendations.

3.1.3 ^{99m}Tc -Phosphonate Radiopharmaceuticals (MDP):

Phosphonate and phosphate compounds localize avidly in bone and, therefore, are suitable for bone imaging. However, phosphonate compounds are more stable in vivo than phosphate compounds because the P-O-P bond in phosphate is easily broken down by phosphatase enzyme, whereas the P-C-P bond in diphosphonate is not. For this reason, diphosphonate complexes labeled with 99mTc are commonly used for bone imaging, methylene diphosphonate (MDP), and hydroxylmethylene diphosphonate (HDP), are most commonly used in nuclear medicine.

Commercial kits for MDP are available from different manufacturers. The composition of each kit varies from vendor to vendor in quantities of the chelating agent and the stannous ions. All 99mTc-diphosphonate agents are weak chelates and tend to degrade with time, producing 99mTcO4 impurity in the presence of Oxygen and free radicals produced by radiations.

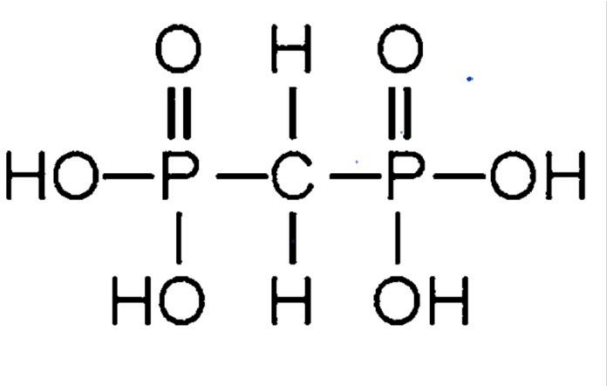


FIGURE 3.1 Molecular structures of methylene diphosphonate (MDP) compounds used in bone imaging.

3.2 Methods of Data collection and data analysis:

The data was collected on a master sheet design for that purpose, different tables used to tabulate the finding which were statically analyzed using SPSS (version 20). The methods of data collection included observation, tests and reference form IAEA

Chapter Four
Results

CHAPTER FOUR

Results

Establishment of National Diagnostic Reference Level for bone Doses in Center A and Center B Nuclear Medicine Department The data in this research is collected form 160 patients who were selected from two centers, who were diagnosed in center B (10) patients and center A (150) patients in nuclear medicine departments and the data represented in tables and figure.

Table 4.1 demographic data for age rang (20-40) and patients dose in mCi at center A.

24 patients (4 male, 20 female)				
	Min	Max	Mean	Std. Deviation
Age	20.00	39.00	33.13	5.236
Wight	35	88	62.71	13.505
Height	147.0	196.0	163.67	10.757
Activity	19.00	30.00	22.17	2.854

Table 4.2 demographic data for age rang (40-60) and patients dose in mCi at center A.

67 patients (12 male, 55 female)				
	Min	Max	Mean	Std. Deviation
Age	40.00	58.00	48.6418	5.50675
Wight	40.00	130.00	67.9851	15.60739
Hight	147.0	187.00	162.4030	8.86953
Activity	18.00	32.00	23.3433	3.13123

Table 4.3 demographic data for age rang (60-80) and patients dose in mCi at center A.

47 patients (26 male, 21 female)				
	Min	Max	Mean	Std. Deviation
Age	60.00	75.00	65.6170	4.66976
Wight	43.00	140.00	72.3191	19.49817
Height	147.00	188.00	167.3404	9.63525
Activity	19.00	32.00	23.7021	3.32915

Table 4.4 demographic data for age rang (80-100)and patients dose in mCi at center A.

12 patients (12 male, 0 female)				
	Min	Max	Mean	Std. Deviation
Age	80.00	86.00	82.67	2.640
Wight	50.00	75.00	62.92	10.04
Height	150.00	177.00	167.75	7.339
Activity	18.00	26.00	21.58	2.466

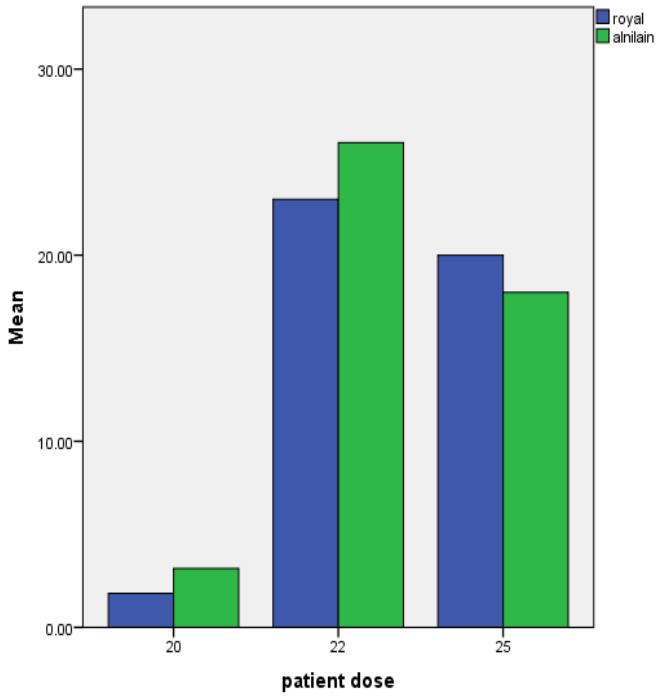
Table 4.5 demographic data for all patient, **dose in mCi at center A**.

150 patients (54 male, 96 female)				
	Min	Max	Mean	Std. Deviation
Age	20.00	86.00	54.200	14.722
Wight	35.00	140.00	68.900	16.53
Height	147.00	196.00	164.5800	9.53
Activity	18.00	32.00	23.130	3.152

Table 4.6 demographic data for all patient, dose in mCi at center B.

10 patients (4 male, 6 female)				
	Min	Max	Mean	Std. Deviation
Age	43	78	56.30	12.789
Wight	49	87	72.10	12.836
Height	154	200	169.50	12.981
Activity	20	25	22.00	1.826

Figure 4.1 show statistical parameters for patient's dose in mCi at center A and center B.



Chapter Five
Discussion , Conclusion and Recommendations

CHPTER FIVE

5.1 Discussion:

The data in this research (Establishment of National Diagnostic Reference Level for bone Doses in center A and center B Nuclear Medicine Department)is collected form 160 patients who were selected from two hospitals, who were diagnosed in center B (10) patients and center A (150) patients in nuclear medicine departments and the data represented in tables and figure.

Table 4.1 show statistical parameter for age rang (20-40) and the variables was age , high, weight and the dose(activity), the values was {mean ± STD} age (33.1250±5.23627), high(163.66±10.7569), weight(62.71±13.506), Dose (22.166±2.85393).

Table 4.2 show statistical parameter for age rang (40-60) and the variable s was age , high, weight and the dose(activity), the values was {mean ± STD} age (48.6418±5.50675), high(162.4030±8.86953), weight(67.9851±15.60739), Dose (23.3433±3.13123).

Table 4.3 show statistical parameter for age rang (60-80) and the variable s was age , high, weight and the dose(activity) and the values was {mean ± STD} age (65.6170±4.66976), high(167.3404±9.63525) weight (72.3191±19.49817) Dose (23.7021±3.32915).

Table 4.4 show statistical parameter for age rang (80-100) and the variable s was age , high, weight and the dose(activity) and the values was {mean ± STD} age (82.3636±2.54058), high(166.9091±7.13379), weight(61.8182±9.75519), Dose (21.2727±2.32770).

Table 4.5 show statistical parameter for all patient in NMDC and the variable s was age , high, weight and the dose(activity) and the values was {mean ± STD} age(54.2000±14.72158), high(164.5800±9.53360), weight (68.0933±16.53321) , Dose (23.1267±3.15228).

Table 4.6 show statistical parameter for all patents in RCIH (10) and the variable s was age , high, weight and the dose(activity) and the values was{mean ± STD} age (56.30±12.789), high(169.50±12.981), weight(72.10±12.836), Dose(22.00±1.826) .

Figure 4.1 show the compare for Dose per mCi in **center A** and **center B** where it's higher in **center A** (23.13) than **center B** (22.00) mCi. show dose distribution which is divided for patients to three groups, the first group received dose 20 mCi are represent (27.03 %), second group received dose 22 mCi are represent (66.67 %) and the third group received dose 25 mCi are represent (6.31 %) from all patients 99mTc-MDP.

5.2 Conclusion:

The study was carried out in order to establish diagnostic reference level for dose (activity) for diagnostic bone system, The data collected form (160) patients in center A and center B, In order to evaluate the radiological risk incurred by patients diagnosed at the Department of Nuclear Medicine (DNM).

The compare for Dose per mCi in center A and center B where it's higher in center A (23.14±3.164) than center B (22.00±1.826) mCi.

The data reveal that the practical reference level activity in center A was (23.14±3.164) mCi and center B was (22.00±1.826) mCi and the result compared with International standard (AAPM) its 26mCi.

At this study 14.375% from all patients tacked dose more than international reference levels activity (26 mCi) because they were obese, therefore the DRL for dose (activity) in the center A & center B will be acceptable if the patient in normal age and weigh. If the patient is overweight we need to increase the dose to the patient.

5.3 Recommendations:

1- Staff of the nuclear medicine must be qualified properly.

2- Establishment of more effective radiation protection systems at the nuclear medicine department in Sudan.

3- All radiopharmaceuticals containers should be put in shields or shielded areas and clearly labeled.

4- All nuclear medicine staff members are recommended to wear lab coats, disposable gloves and face masks during elution and dispensing of radiopharmaceuticals .

5- Work surfaces in the hot lab should be covered with absorbent materials to absorb any possible radioactive spillage contamination.

6- QC for the generator and the gamma camera should be regularly.

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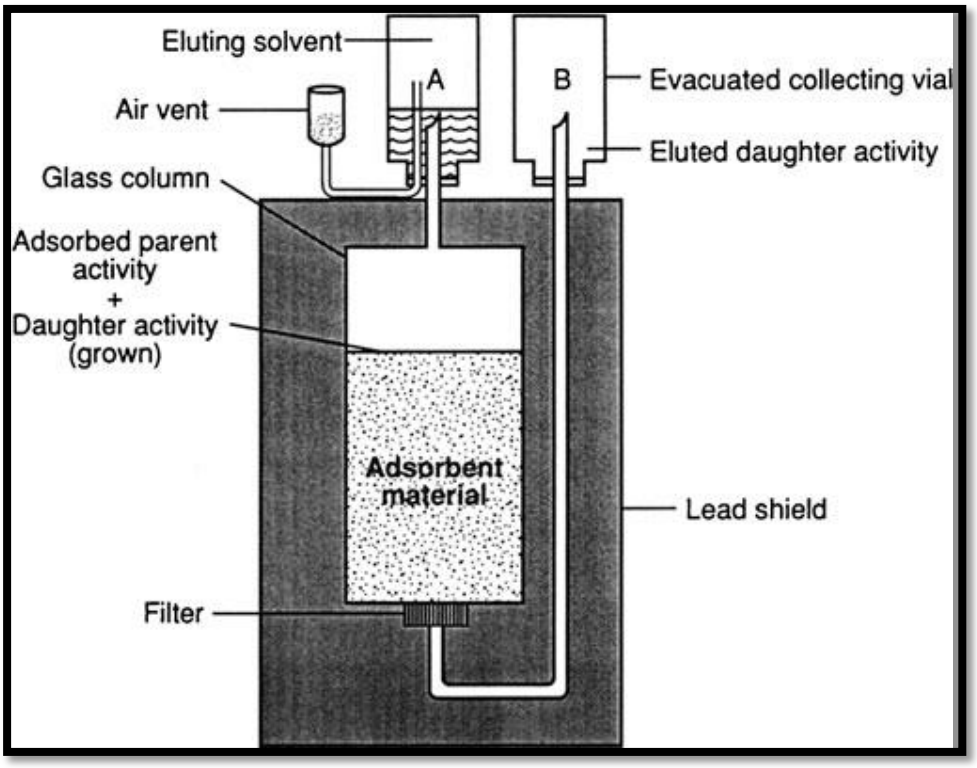
Appendix

Appendix:

Radionuclide generator:



Dose calibrator: