College of Chemical Pathologists of Sri Lanka

CCPSL NEWSLETTER

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COVER STORY

8th Annual Academic Sessions (AAS) 2023
College of Chemical Pathologists of Sri Lanka
ADVANCING THROUGH CHALLENGES

Editors

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Message form the President (2022/2023)

Dr. Dulani Jayawardana
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Dear Esteemed Members of the College of Chemical Pathologists of Sri Lanka (CCPSL),

I extend my deepest gratitude to our diligent editors whose tireless efforts have brought forth the 5 th edition of our newsletter. This platform continues to be a beacon for the sharing of knowledge, research, and creative expressions. To our vibrant and talented members, I encourage you to embrace this opportunity to contribute your insights and perspectives. Let us nurture a culture where the richness of our collective intellect and creativity flourishes.

Reflecting on the past year, we have successfully reinstated our regular programs, introducing new initiatives to enrich educational opportunities for our members. Collaborations with other specialties and international faculties have not only expanded our horizons but have also underscored the vital role of Chemical Pathologists in the medical landscape of our country. Together, we have enhanced our global recognition.

I extend my heartfelt invitation to each member to cultivate the habit of writing and to actively engage in the shared journey of knowledge dissemination. Your participation is integral to the continued success of CCPSL, and I am confident that together, we will scale new heights.

Looking forward, our collective aspiration is to inaugurate our own journal, and I am pleased to report that the groundwork for this endeavor is well underway. I am confident that our members will actively participate in shaping the very first journal of CCPSL, thereby contributing to its success and establishing it as a valuable resource in our field.

As we advance, let us uphold the values of excellence, collaboration, and continuous learning. Our collective efforts will undoubtedly shape the future of Chemical Pathology in Sri Lanka and beyond.

Thank you for your unwavering commitment and support.

Warm regards,
Dr Dulani Jayawardana
President, College of Chemical Pathologists of Sri Lanka

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CCPSL NEWS

Induction of the 8th President of CCPSL and Inauguration Ceremony of Annual Academic Sessions of CCPSL 2023

The induction of the 8th President of the College of Chemical Pathologists of Sri Lanka and the inauguration of the 8th Annual Academic Sessions, 2023 was held on 14th and 15th July, 2021 at the Grand Kandyan Hotel, Kandy.

The inauguration ceremony was a great success and this event was witnessed by a large number of participants.

The chief guest for the occasion was Dr Asela Gunawardena, Director General of Health Services, Ministry of Health, Nutrition and Indigenous Medicine.

Dr Dulani Jayawardana was inducted as the 8th President of CCPSL by the immediate Past President, Dr Kisali Hirimutugoda. The presidential address was delivered by Dr Dulani Jayawardana highlighting the importance of the Chemical Pathology services in managing patients and the role of the Chemical Pathologist.

Professor Neelakanthi Vajira Ratnatunga, Consultant Histopathologist, Faculty of Medicine, University of Peradeniya Sri Lanka, was awarded the CCPSL fellowship in recognition of her exceptional contributions to the field of Pathology and her dedicated service as a healthcare leader, distinguished academic, and exemplary teacher.

Mr. Muthalibu Muhammed Hunais, Principal at School of Medical Laboratory Technology, Peradeniya, was felicitated for his remarkable achievements and valuable contributions to the field of Medical Laboratory Technology.

The prestigious CCPSL oration for the 2nd time titled "**A Lifetime of Learning**" was delivered by Dr Ken Sikaris, Consultant Chemical Pathologist Melbourne Pathology, Australia.

At the end of the inauguration the audience was entertained by a musical event.
The ceremony concluded with a grand reception.

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CCPSL NEWS

8th Annual Academic Sessions of CCPSL

The 8th Annual Academic Sessions of the CCPSL was successfully concluded at the Grand Kandyan Hotel, Kandy on 14th and 15th July, 2023 after 2 days of new knowledge under the theme of "**Advancing Through Challenges**."

The scientific programme included two parallel programmes, academic and medical laboratoryscience (MLS), extending for 2 days. In the academic programme, there were ten plenaries and five symposia covering a wide range of timely and important topics of Chemical Pathology.

Thirty four resource persons contributed to the 8th Annual Academic Sessions and there were 12 overseas speakers who shared their knowledge and experience generously. The topics relatedto laboratory management, hypertension, inborn errors of metabolism (IEM), investigations in renal diseases and quality assurance in total testing process were discussed in symposia.

This event was an excellent gateway for Chemical Pathology trainees and other researchers to presenttheir research work. There were 48 abstracts and out of them 12 were chosen for oral presentationwhile the rest were displayed as e-posters.

The oral presentation competition was conducted on a pre-scheduled date prior to the main programme andjudged by imminent researchers in the field. The main objective was to develop research interest and presentation skills among Chemical Pathology and MLS trainees. The winners of the oral presentationand e-poster competition were announced at the closing ceremony.

The 2023 AAS – CCPSL clinical Lab Expo was open on both days for all attendees of the mainprogramme and also for non-registered laboratory professionals who were interested to learn aboutlatest diagnostic technologies and laboratory medicine developments. It gave them the opportunityto interact with the exhibitors in person and find solutions to laboratory related needs.

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Winners of the awards - 8th Annual Academic Sessions of CCPSL

Oral Presentations (Research and Audits Category)

First place

Assessment of the Correlation of Haemoglobin A1c and Serum Fructosamine with Mean Blood Glucose Level in Diabetic Patients with Chronic Kidney Disease in a Tertiary Care Hospital of Sri Lanka

Puliyadda TMNK

Department of Chemical Pathology, Colombo North Teaching Hospital, Sri Lanka

nadeera25@yahoo.com

Second place

Efficacy and Effectiveness of Adrenal Venous Sampling in the Management of Primary Aldosteronism; Single Centered Cohort Study at a Tertiary Care Hospital in Sri Lanka

Balasooriya BMCM

Department of Chemical Pathology, National Hospital of Sri Lanka

menaka1989balasooriya@gmail.com

Third place

The Association between Inflammatory Markers and Outcomes among Covid-19 Patients Admitted to Intensive Care Units at a Tertiary Care Hospital in Sri Lanka

Liyanage TDG

Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, General Sir John KothelawalaDefence University, Sri Lanka

thathsaraniliyanage890@gmail.com

Oral Presentations (Case Report Category)

First place

Shedding Light on Parathyroid Adenoma in Pregnancy: The Success of Parathyroid Hormone Assay in Fine Needle Aspirate: A Case Report

Galmangodage NE

Departtment of Chemical Pathology, National Hospital of Sri Lanka, Colombo

ne.galmangodage@gmail.com

Second place

Adenine Phosphoribosyl Transferase (APRT) Deficiency Presenting as a Rare Inherited Etiology of Nephrolithiasis: First Sri Lankan Case Report

De Silva MMN

Department of Chemical Pathology, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka

Nishadesilva29@gamil.com

Third place

Risk of Ignoring Chronic Diarrhoea; A Patient with Carcinoid Tumour

Madurangi DWDD

Department of Chemical Pathology, National Cancer Institute, Maharagama, Sri Lanka

dinidenipitiya@gmail.com

E-Poster Presentations (Research and Audits Category)

First place

Association of Lead and Redox Sensitive Transcription Factors in Occupationally Pb Exposed Population

Sharma S

Department of Biochemistry, All India Institute of Medical Sciences Jodhpur, India

shailjachambial@yahoo.com

Second place

An Evaluation of the Internal Quality Control Performance of the General Biochemistry Analytes in a Laboratory of a Tertiary Care Hospital of Sri Lanka

Puliyadda TMNK

Department of Chemical Pathology, Colombo North Teaching Hospital, Sri Lanka

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Third place

Relationship between Serum Total Prostate-Specific Antigen and Sonographic Findings of the Prostate in a Group of Men with Benign Prostatic Hyperplasia

Saranasinghe HRNC

Department of Medical Laboratory Science, Faculty of Allied Health Sciences, University of Ruhuna

Chandramalisaranasinghe11@gmail.com

E-Poster Presentations (Case Report Category)

First place

Case Report of a Child with Seizures and Skin Lesions; What to do with Biotin

Arooran T

Department of Chemical Pathology, Lady Ridgeway Hospital for Children, Borella, Sri Lanka

thayaniarooran@gmail.com

Second place

First case report of testosterone assay-negative interference in a female with virilization

Balasooriya BMCM

Department of Chemical Pathology, National Hospital of Sri Lanka

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Third place

A Case of Unresolved Hypercortisolism; A Diagnostic Dilemma

Sujeeva N

Department of Chemical Pathology, National Hospital of Sri Lanka

HDL-Cholesterol over 100mg/dL: Good or Bad?

Dr Saroja Siriwardene
Consultant Chemical Pathologist

Introduction

High-density lipoprotein cholesterol (HDL-C) has for decades enjoyed being the **"Good Samaritan"** of an individual's lipid profile. With multi-centric research endorsing the cardiovascular benefits of higher HDL-C values, there is little wonder that people try to improve on it, for good cardiac health.

However, what impact would an extremely high HDL-cholesterol level have on an individual?

(a) Is the benefit limited or unlimited?

(b) Could it be detrimental?

Main Function of HDL

High-density lipoprotein (HDL) particles serve the important role of reverse cholesterol transport. This process allows excess tissue cholesterol, to be removed via macrophages which transfer cholesterol from cell membranes to HDL particles to be excreted from the body in bile [5].

History of HDL Estimation

By definition, HDL-particles have a density ranging from 1.063 – 1.210. Historically HDL was demonstrated by ultra-centrifugation of the sample and harvesting the fraction with the given range of density for gravimetric estimation 2. This method is limited to research because of the cost of equipment and the cumbersome nature of the procedures involved.

For routine laboratory purposes, the HDL particles therefore need to be isolated from the rest, using simpler technology. The isolated HDL fraction is not measured in its entirety. Instead, either the protein moiety or the lipid moiety is measured as an indirect means of quantifying HDL [2]. HDL is composed of approximately 50% proteins (predominantly Apo A-1). The phospholipid content is the largest lipid by mass (30%) with cholesterol and its esters contributing about 20% [3].

What Do We Mean by HDL-Cholesterol Measurement?

HDL-C measurement is a cheap substitute for the number of HDL particles carried by a unit volume of plasma. In the absence of facilities for reference methods for measuring the HDL particles, the routine clinical chemistry laboratory has resorted to give an estimate by measuring only the 20% cholesterol constituent carried by all the HDL particles put together. This is reported as the HDL-C level in serum. It does not provide a breakdown of the HDL particle type, size or their distribution in plasma.

The Goal of HDL-Cholesterol Measurement

The goal is to find out how many milligrams (or millimoles) of cholesterol are carried by the HDL particles found in 100 mL (or 1 litre) of plasma. This becomes a tall order when one considers the fact that plasma would normally contain a mixture of multiple lipoprotein particles: viz high-density (HDL), low-density (LDL), intermediate-density (IDL), very-low-density (VLDL) and lipoprotein "**a**" (Lpa) with chylomicrons being present in non-fasted samples.

Second Generation HDL-Cholesterol Assays

Due to poor isolation techniques used in the past, the HDL-C measurement has taken a bumpy ride over the decades. The second generation HDL-C assays use combinations of polyanions and divalent cations to selectively precipitate Apo-B-containing lipoprotein particles (e.g. Heparin-$MnCl_2$, dextran sulphate-$MgCl_2$ and Na phosphotungstate[2]). Following centrifugation, the cholesterol content of the supernatant will be the HDL-C level, and hence represent the HDL particles. Various precipitants perform differently, with incomplete precipitation leading to an over-estimation of HDL-C. Assays have subsequently been optimized by using the reagent, instrument and calibrator from the same supplier [3] .

Third Generation HDL-Cholesterol Assays

A major breakthrough in HDL determination was reported in 1994 with publications of the homogeneous methods that are capable of full automation [3] . With the elimination of manual pre-treatment steps, precision improved greatly. In these methods, the cholesterol in non-HDL particles is "**masked**" with (anti-apo B) antibodies, polymers or detergents, allowing the cholesterol in the HDL component to be determined enzymatically [5] .

Homogeneous assays were initially introduced to Sri Lanka at the turn of the new millennium. The majority of medical testing laboratories in the world have adopted them even though questions have been raised regarding their specificity, especially in specimens with unusual lipoprotein compositions [2] . Deviations from reference methods have been observed in the presence of high triglycerides, at low HDL values and in the presence of atypical lipoproteins [5] .

Influence of HDL-C on Calculated LDL-C Report

The determination of HDL-C by itself is hardly affected by prior consumption of food [5] . However, a 12-14 hour fast allows chylomicrons to be metabolized, which otherwise interfere with the triglyceride assay in a lipid profile. LDL-cholesterol is calculated using the **Friedewald formula** [1] which is validated for samples having a serum triglyceride level <400 mg/dL. When all results are in mg/dL;

LDL cholesterol = Total cholesterol – HDL cholesterol – (Triglycerides/5)

Accordingly, errors in HDL-C measurement will adversely affect the calculated LDL-C level, which is the target of therapy for hyperlipidaemia. Falsely high HDL-C can falsely reduce the calculated LDL-C and vice versa. For samples with triglycerides between 400 – 2000 mg/dL, direct estimation of LDL-C (Direct LDL-C test) is recommended.

Alternatives for HDL and LDL Particles

HDL-C and LDL-C analysis could be replaced by the determination of Apo A1 and Apo B respectively. These assays can be readily standardized and are not significantly distorted by high triglycerides. In addition, Apo B reflects all atherogenic lipoproteins taken together [5] .

Sub-classes of HDL Particles

Discrete HDL particle sub-classes have been identified on the basis of differences in size or charge, including two major ultracentrifugation sub-classes HDL_2 and HDL_3 . HDL_2 is larger and thought to be more cardio-protective [4] . Double precipitation methods with polyanions or nuclear magnetic resonance (NMR) spectroscopy could quantify HDL sub-fractions [2,5] .

Personal Experience in Reporting Very High HDL-Cholesterol

Our hospital laboratory caters to in-patients, out-patients and screening for non-communicable diseases in the community. We use a homogeneous method using reagent, calibrator and instrument from the same source and practice meticulous internal quality control and external quality assurance (EQA) procedures. Periodically we encountered very high HDL-cholesterol levels. The test was repeated in 1:1 dilution for values above the Analytical Measurement Range (AMR) for HDL-C, in order to issue the final result. Although we received an occasional negative feed-back comment from some clinicians, we were encouraged by the success of the EQA results on samples having HDL-C as high as 120 mg/dL.

From routine fasting lipid profiles performed from 2014 -2018 and available in the laboratory information system (LIS), we identified 445 individuals having HDL-C levels >100 mg/dL (with the total cholesterol <300 mg/dL) [6] . The male: female ratio was 1:4. 42% of the total were females >60 years old.

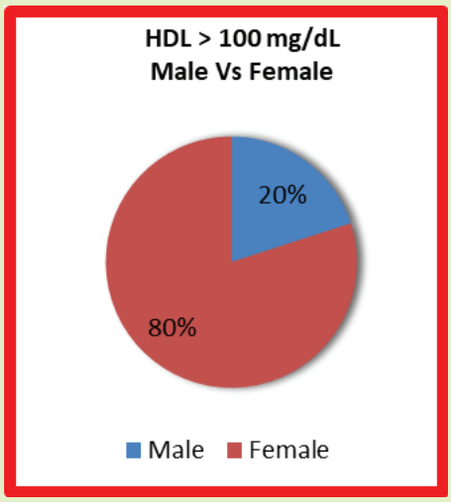

Figure 01
Distribution according to gender

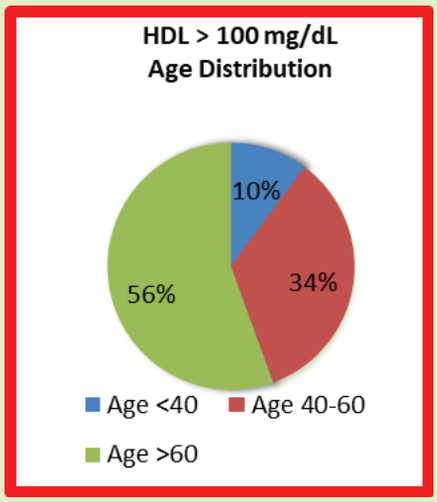

Figure 01
Distribution according toage

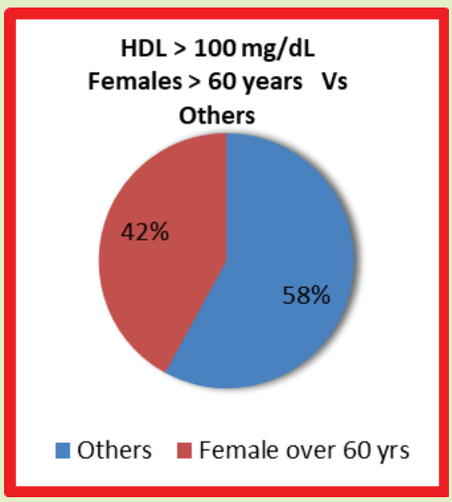

Figure 01
Distribution according toFemales > 60 years Vs. others

The highest HDL-C was 167 mg/dL (median 105). (The gender ratio and the median HDL-C value are comparable to some of the published literature[9, 10, 11]).

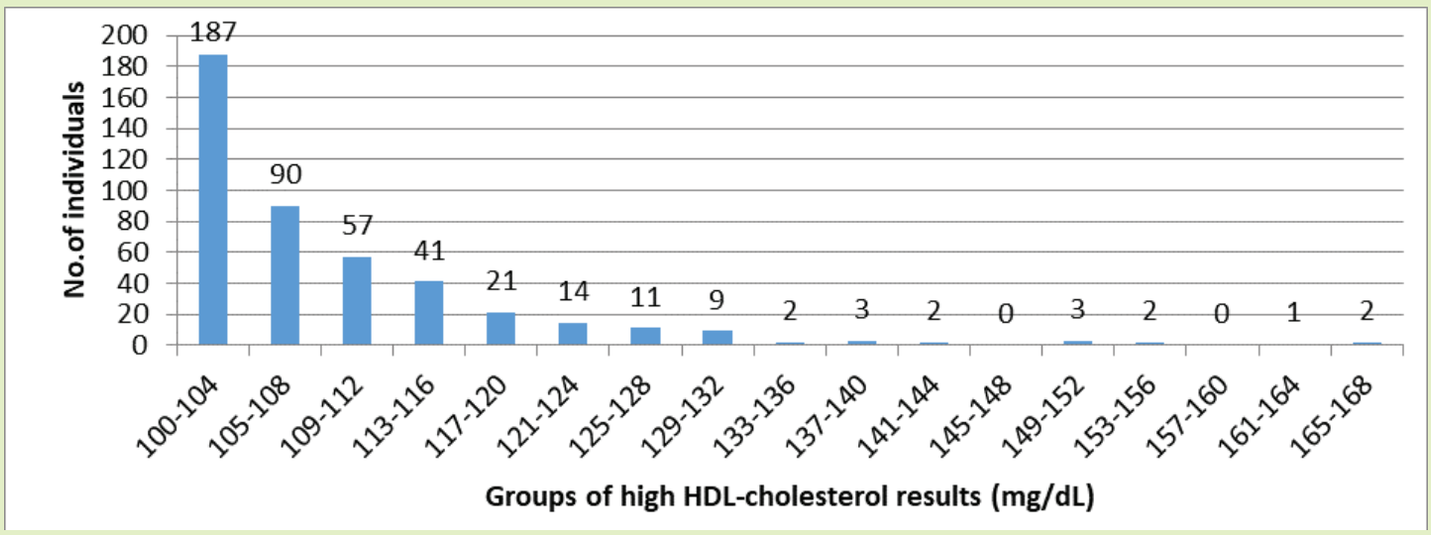

Figure 04: Distribution of invidividual values of HDL- C >100 mg/dL

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The variability of HDL-C on those who had multiple lipid profiles on record was low (median 6%), indicating that it was a relatively stable parameter in serum over time. However, the LIS cannot identify those repeating the test using the name differently, which could potentially over-estimate the total number

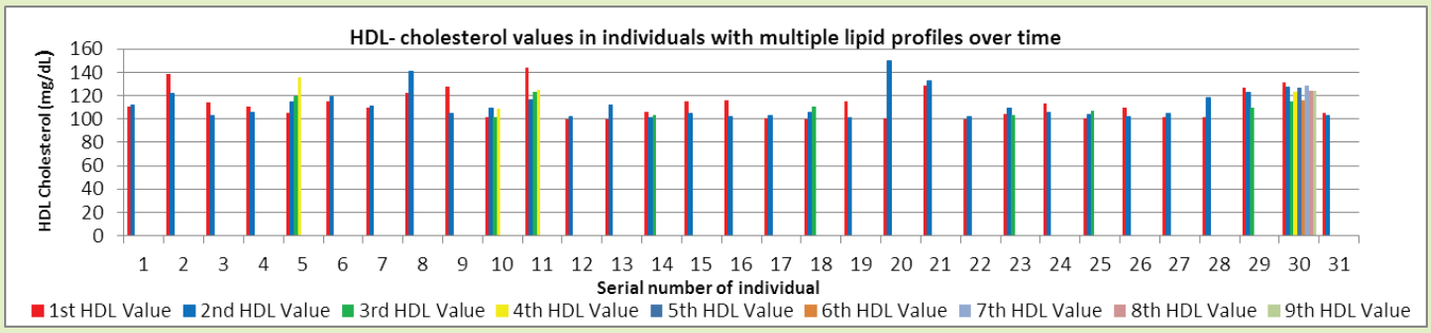

Figure 05: HDL-cholesterol values in individuals with multiple lipid profiles over time.

Are We Seeing More Individuals with Very High HDL-C Now?

Probably we identify individuals with very high HDL-C better and with more confidence now. In the past, a very high HDL-C was often considered a laboratory error both by clinicians and laboratory technicians carrying out the manual precipitation method. The laboratories were often not supported by adequate EQA for HDL-C. The focus was on reporting accurately in the 30 – 60 mg/dL range. Laboratory standards have definitely improved since then.

Is Very High HDL-C Clinically Important?

There is emerging evidence that very high HDL-C in an individual is a clinically important finding. Recent research has shed light on a paradoxical increase in morbidity and mortality in individuals with very high HDL-C values[7, 8, 9, 10, 11]. Therefore we need to understand the high-HDL-C burden in our community too and carefully evaluate them.

A publication based on the IDEAL and EPIC-Norfolk studies concludes that very high plasma HDL-C (>70 mg/dL) and very large HDL particles are associated with an increased risk of coronary artery disease (CAD)8. In this study, those with HDL-C >80 mg/dL in IDEAL and >97 mg/dL in EPIC were evaluated as one group, with no further subdivisions. The prevailing view that large particle size confers a lower CAD risk, was disputed by this study which measured particle size using NMR spectrometry. However, Apo-A1 remained protective across the major part of its distribution and more uniformly represents lower risk.

Wijesundera et al endorsed in a CANHEART sub-study in 2017 that they observed an inverse relationship of HDL-C with both cardiovascular and non-cardiovascular outcomes and regarded low HDL-C a marker of poor overall health. They too evaluated all those >90 mg /dL of HDL-C as one group.[10]

Similarly Wilkins et al reported a plateau effect for CHD risk at very high levels of HDL-C and believe that they are at least partially identifiable through assessment of traditional risk factors.[11]

Interestingly, in a study on a large cohort of individuals (116,508) from the general population in Denmark, Madsen et al observed that the association between HDL-C and all-cause-mortality was **U-shaped**, with both extreme high and low HDL-C being associated with high mortality.[9] The HDL-C level associated with the lowest risk for all-cause-mortality was 73 mg/dL for men and 93 mg/dL for women. This study had better categorization of individuals with 97-115 mg/dL (n=5795), 116-134 mg/dL (n=1109) and > 135 mg/dL (n=218) as separate groups. Those >97 mg/dL comprised 6.1% of the total subjects. One likely explanation for the U-shape was that genetic variants associated with both high risk of CAD and high HDL-C may play a role (e.g. mutations in CETP, ABCA 1, LIPC and SCARB 1).

Future of Individuals with Very High HDL-Cholesterol

Those with very high HDL-C need to be identified by using an assay with proven quality as well as performance of dilution tests whenever the result is above the cut-off for AMR as verified by the laboratory periodically. There is evidence to indicate that once identified, they too should to be evaluated for both cardiac and non-cardiac health. Pertinent tests include direct LDL-C measurement, Apolipoprotein A-1, Apo A-1/B ratio, HDL sub-classes and genetic mutation studies amongst others. In the past, such individuals were reassured as belonging to a group with low risk for CAD. However, with the current evidence available to us, we can no longer dismiss them placidly!

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Beyond the Traditional Lipid Profiles in Chronic Kidney Disease

Dr Chandrika Meegama
Consultant Chemical Pathologist

Cardiovascular morbidity and motility in chronic kidney disease (CKD) patients remain unacceptably high, as evidenced by large epidemiological studies and registries of renal patients' world –wide. CKD patients have accelerated atheromatosis and ischemic events from early stages of the disease. Both etiology and clinical manifestations have differential aspects compared to the general population. However, contrary to the general population, the implications of lipid alterations are controversial.

First, the lipids of patients with CKD show a different profile from the dyslipidemia of the general population, and it varies with the severity of renal dysfunction. In CKD, lipid abnormalities are characterized by hypertriglyceridemia, variable levels of LDL-cholesterol and low levels of HDL-cholesterol. In early CKD stages, there are high levels of LDL-cholesterol, but in more advanced stages this parameter is normalized or even reduced. The National Observatory of Atherosclerosis in Nephrology (the NEFRONA Study) observed a progressive decrease of total cholesterol, LDL-cholesterol, HDL-cholesterol and non-HDL-cholesterol that are proportional to the stage of renal disease.

Second, renal patients have a higher burden of atheromatosis than the general population, and it increases with the severity of renal dysfunction. In addition, they show a more rapid progression of atherosclerosis, particularly in advanced CKD stages.

Third, studies on therapeutic interventions increased the controversy. Statins, lipid-lowering drugs with highly demonstrated effectiveness in the general population, appeared to be less effective in patients with CKD. The well-known studies 4D7 and AURORA 8failed to demonstrate the effectiveness of statins in dialysis patients. In addition, the SHARP study reinforced this idea, although it showed that in non-dialysis CKD patients, statins did reduce vascular risk. However, this reduction decreased as renal function declines.[1]

In addition, a debate has been generated by the latest American guidelines of vascular risk, which were also supported by the 2013 KDIGO guidelines on the management of dyslipidemia in CKD. They encourage the use of pharmacological treatment based on the patient's risk profile and omitting LDL-cholesterol values. The guidelines are summarized in the following points. First, it is recommended to study the lipid profile of all patients with CKD of any stage. Most do not require follow-up controls. Second, it is recommended to initiate statin or statin / ezetimibe in CKD patients over 50 years of age not on dialysis. Third, in patients under 50 years of age not on dialysis and renal transplants of any age, it is suggested to treat only if they have a history of cardio or cerebrovascular event, diabetes or an estimated 10-year risk of cardiovascular event greater than 10%. In both cases, the indication for treatment is not guided by LDL-cholesterol level, and dyslipidemia follow-ups are not recommended. Finally, in patients on dialysis, it is not suggested to initiate lipid-lowering treatment.[2]

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In CKD patients, the nearly normal or low levels of LDL-cholesterol do not explain the fast progression and elevated atheromatous burden, and the considerable residual risk.[3] Nowadays, there are new approaches to analyze the different subpopulations of lipoproteins; among many options, the most common are: gel electrophoresis, density gradient ultracentrifugation and nuclear magnetic resonance.[4] Briefly, each method determines different physicochemical parameters of lipoproteins such as size, electrical charge, cholesterol concentration or the magnetic resonance to assess the lipoprotein subclass distribution.[5]

The parameter "LDL-cholesterol" or "HDL-cholesterol" reflects the concentration of cholesterol transported in molecules called LDL or HDL, respectively. However, cholesterol may be transported in a variable number of LDL or HDL particles, thus the load of cholesterol per particle would not be the same. Therefore, it makes sense, to measure the concentration of LDL and HDL particles (LDL-P and HDL-P); individuals with the same LDL-cholesterol may have different vascular risk if they have different particle concentration. The individual with higher LDL-P has higher cardiovascular risk.[6] Multiple studies have shown that small LDL particles are more atherogenic than large ones since they have an increased ability to penetrate the vascular wall.[7]

Similarly, small HDL particles also correlate with a higher vascular risk due to a decreased anti-atherogenic effect.[8] Renal patients have an accumulation of small LDL particles that are associated with a higher rate of cardiovascular events.[9,10] Interestingly, they show a decrease in small pro-atherogenic HDL particles. Paradoxically, these parameters of considerable clinical relevance are currently not determined in daily clinical practice although their use in research is becoming widespread.

Lipoprotein (a) [Lp (a)] is one parameter easy to obtain from the clinical Lab. It has been demonstrated that the levels of Lp (a) increase as kidney disease progresses and decline after kidney transplantation.[11,12] An in vivo study showed a decrease in the clearance of Lp (a) in hemodialysis patients, demonstrating the involvement of the kidney in its elimination. Unlike patients on hemodialysis, patients with nephrotic syndrome have an increased hepatic synthesis of Lp (a) resulting in an elevation of plasma levels. Lp (a) has a marked proatherogenic effect Lp (a) predicts the development of carotid atheromatous disease and vascular events in dialysis patients. However, the determination of Lp(a) is not widespread, which can be explained by the absence of drugs capable to modify Lp(a) levels.

New drugs like PCSK9 inhibitors offer a new therapeutic approach. They have the ability to reduce of LDL cholesterol levels and the risk of vascular events.[13] Moreover; they also reduce the plasma concentration of Lp (a). It should be emphasized that these new drugs exert an impact on the size of the particles. They reduce the total concentration of LDL particles and also cause a reduction of large and small LDL particles. Surprisingly, they increase the number of HDL particles, especially the larger ones.

Meanwhile, it is urgent to gain further information about specific lipid abnormalities in renal patients. Besides the quantitative changes described above, CKD is characterized by qualitative changes caused by a highly inflammatory and pro-oxidative state.[14] New research tools, such as metabolomics and lipidomics, are useful to investigate lipid abnormalities in CKD patients.

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Uric acid: An Indispensable Analyte to Screen Purine Pathway Defects

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Abstract

Altered uric acid levels in both serum and urine is an indispensable marker in the detection of purine pathway disorders. The diagnosis of purine pathway defects may be overlooked due to variable clinical presentations. Uric acid, a compound that can be easily analyzed, may be the initial indicator to perform confirmatory tests for purine pathway defects. This article highlights the pathophysiology of uric acid and some of the purine pathway defects that can be easily detected in a Chemical Pathology laboratory.

Uric acid (UA) (2,6,8 trioxypurine C5H4N4O3, molecular weight 168 Dalton), a nitrogen containing compound, is the final product of purine metabolism in humans. Liver and intestines are the major sites of its synthesis. Being a weak acid (pKa 5.8) UA exists as urate at a physiological pH. Approximately two thirds of uric acid are excreted via kidneys while the remainder is eliminated through the intestines. 90 % of freely filtered uric acid is absorbed [1].

A Chemical Pathology laboratory should play a detective role by introducing easily quantified analytes to the routine general biochemistry test panel to screen inborn errors of metabolism (IEM). UA is one such wonderful analyte. Altered levels of UA may indicate some of the purine pathway defects in unexplained clinical manifestations [2]. Inherited disorders of purine metabolism have a high clinical impact with a wide array of clinical presentations involving different medical specialties mainly neurology and renal [2,3].

Following are some of the purine related and non-purine related IEM, with altered UA levels in serum and urine.

Purine pathway related IEM [4,5]		
Hyperuricaemic hyperuricosuria		
Disease	Symptoms	Biochemical Changes (Purine pathway related)
5-phosphoribosyl-1-pyrophosphate synthetase over activity	Early onset: Sensorineural hearing impairment and neurodevelopmental delay Late juvenile: Urolithiasis or gout without neurological signs	Serum ↑ UA Urine ↑ UA
Hypoxanthine-guanine phosphoribosyl transferase deficiency	Complete deficiency Lesch-Nyhan syndrome (LNS): Spasticity, self-mutilation, choreoathetosis, haematuria Partial deficiency Kelley-Seegmiller syndrome: Early adult onset, gouty arthritis some may have symptoms of LNS	Serum ↑ UA Urine ↑ UA Serum ↑ or normal UA Urine ↑ UA

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Hypouricaemic hypouricosuria		
Xanthinuria (xanthine oxidase deficiency)	Urolithiasis, haematuria and recurrent urinary tract infections	Serum ↓ UA Urine ↓ UA, ↑ Xanthine ↑ Hypoxanthine
Molybdenum cofactor deficiency (xanthine oxidase and sulphite oxidase deficiency)	Intractable seizures, feeding difficulties, microcephaly [6]	Serum ↓ UA Urine ↓ UA, ↑ Xanthine ↑ Hypoxanthine ↑ Sulphocysteine
Purine nucleoside phosphorylase deficiency	Recurrent infections due to impaired cellular immunity, neurological deficits	Serum ↓ UA ↑ Inosine ↑ Guanosine Urine ↓ UA ↑ Inosine ↑ Guanosine
Non-purine pathway related IEM [4]		
Hypouricaemic hyperuricosuria		
Hereditary renal hypouricaemia	Most are asymptomatic. Can present with haematuria [7], acute kidney injury following physical exercise and rarely childhood stroke [8]	Serum ↓ UA Urine ↑ UA
Fanconi syndrome	Symptoms vary with the cause. Examples of IEM causes for Fanconi syndrome are cystinosis, Lowe syndrome[9], galactosaemia, tyrosinaemia and Wilson disease	Serum ↓ UA Urine ↑ UA
Hypouricaemic hyperuricosuria		
Glycogen storage disorder type 1 (von Gierke)	Hepatomegaly, hypoglycaemia, short stature	Serum ↑ UA Urine ↓ UA
Familial juvenile hereditary nephropathy	Gouty arthritis, rapid progressive renal failure, renal stones at an early age	Serum ↑ UA Urine ↓ UA

To interpret UA, it is essential to consider age and sex matched reference ranges, diet, intake of medications, the presence of ketosis, lactic acidosis and renal failure. Children may have normal serum UA level despite its overproduction due to higher UA clearance, hence normal serum UA doesn't exclude hyperuricaemia. Bacterial contamination elevates urine UA due to rapid degradation of purine nucleosides and bases [10].

Conclusion

Uric acid is an important analyte that should be included in the general biochemistry panel to screen for inborn errors of metabolism, especially in patients with unexplained neurological defects.

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Performance of Biochemical Part Myeloma Defining Events in the Diagnosis of Multiple Myeloma: A Retrospective Tertiary Care Experience

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Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and 10% of all hematological malignancies.[1] In India, The incidence of MM is 0.3-1.9/100,000 and 0.4-1.3/100,000 in males and females.[2] The clinical course of MM almost always starts with the pre-malignant phase of Monoclonal Gammopathy of Undetermined Significance (MGUS) and progresses through Smouldering Multiple Myeloma (SMM) to MM.[3,4]

MGUS shows a monoclonal band which measures <30 g/L and bone marrow plasma cell <10% yet lacks end-organ damage and needs surveillance without any therapy. However, since the disease definition and the diagnostic criteria of MM include CRAB features: **C** (Hyper**C**alcemia), **R** (**R**enal insufficiency), **A** (**A**naemia) and **B** (**B**one lesions), at the time of diagnosis, patients suffer from one or more end-organ damage which is attributable to MM.

Whereas SMM is an intermediate stage, characterised by a lack of end-organ involvement, in contrast to MGUS, SMM has a paraprotein concentration of ≥30 g/L and bone marrow plasma cells of 10%-60%. As a result, the definition of SMM was given as a continuum from pre-malignant MGUS to MM without the appearance of end-organ damage. However, it was noticed a group of SMM the so-called **"Ultra-high risk"** group, develops to MM rapidly as compared to others.1 In view of identifying the cohort of SMM which progresses rapidly to MM, International Myeloma Working Group (IMWG) criteria was revised and upgraded with new biomarkers in 2014 referred to as SLiM CRAB criteria. In addition to CRAB features, SLiM CRAB criteria include: Bone marrow clonal plasmacytosis ≥60%, involved/uninvolved free light chain (FLC) ratio of 100 along with involved FLC is ≥100 mg/L or >1 focal lesion on magnetic resonance imaging.[1,5]

Materials and Methods

In this study we aimed to analyze the performance of the biochemical parameters of the CRAB and newer biomarker in the myeloma defining event which was included in the revised myeloma working group criteria: Involved uninvolved free light chain ratio.

All the newly diagnosed MM patients were included at the KDAH during the period from January 2022 to May 2023. The clinical and biochemical parameters at the presentation were analysed retrospectively.

The diagnosis of MM was made based on the Revised International Myeloma Working Group diagnostic criteria and the clonality of the plasma cells was assessed based on flow cytometry with kappa or lambda light chain restrictions.

Staging of the disease was done according to the International Staging System (ISS).

Results

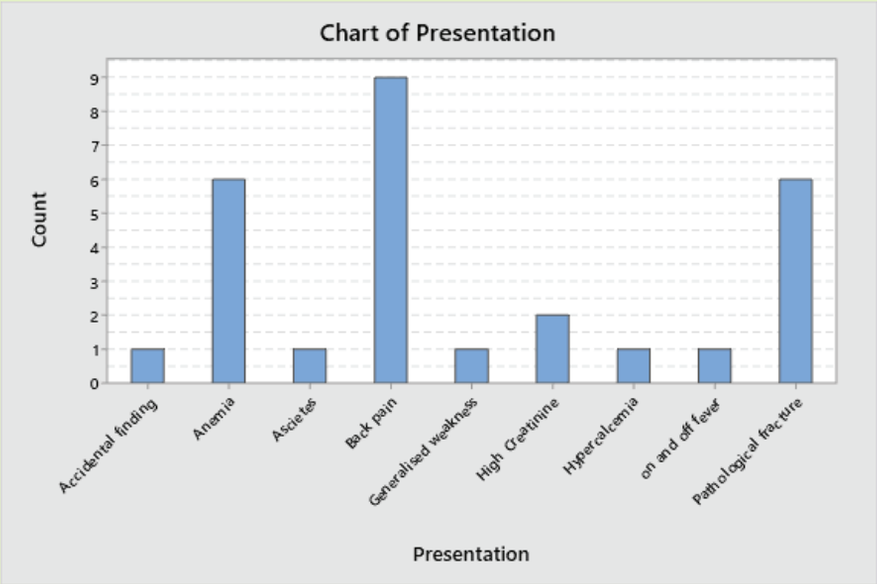
Totally 31 patients were diagnosed during the specified period. The clinical and biochemical data of all those patients were reviewed. Our cohort contained 19 males and 12 females with a male-female ratio of 1:6.

The mean age was 68 years with the range of 44 – 86 years. Around 39% of the patients were above 70 years old whereas we had one female who was 44 years at the time of diagnosis.

The descriptive statistics of the patients are highlighted in Table 1.

	Mean	SD	Minimum	Maximum
Age (Years)	68	9.64	44	86
Albumin adjusted Calcium (mg/dL)	9.5	2.063	7.7	13.2
Creatinine (mg/dL)	1.43	1.098	0.44	5.8
Kappa - Lambda Ratio	73.0	164.5	0.003	743.6
Involved - uninvolved free light chain ratio	94.6	165.0	1.0	743.6
Beta – 2 Microglobulin (mg/L)	8.26	5.66	1.24	20.80
Total Protein (g/dL)	8.1	1.715	5.1	13.4
Albumin (g/dL)	3.5	0.707	2.3	4.9
Globulin (g/dL)	4.6	1.373	2.7	8.6
Albumin: Globulin	0.8	0.2430	0.45	1.34

The most common presenting complaint was back pain without associated pathological fractures in 9 patients (29%) followed by pathological fractures and investigated for anemia in 6 patients each (19%). The most common site of pathological fracture is vertebrae (3/6) (Figure 1).



In the trephine biopsy of the bone marrow, monoclonal plasma cells ranged from 15% to 80%. In our analysis of general biochemical parameters, 24 out of 31 (77.4%) patients had albumin to globulin ratio <1 which is the lower level of the reference interval applied in our laboratory. Although the majority of the patients had lytic lesions and or pathological fractures, only 18% of the patients showed albumin-adjusted calcium levels >11 mg/dL. However, around 31% of the patients had albumin-adjusted calcium levels above the reference interval of 10 mg/dL. Only 5 out of 31 patients (16.1%) had creatinine levels of >2 mg/dL. In 84% of the patients, para-protein migrated to the gamma region and we had monoclonal bands at beta 2 and beta 1 regions as well. (Figure 2) In serum protein electrophoresis, the most common heavy chain and light chain are IgG and kappa respectively and around 58% of the cases had IgG-kappa subtype of immunoglobulin. (Figure 3)

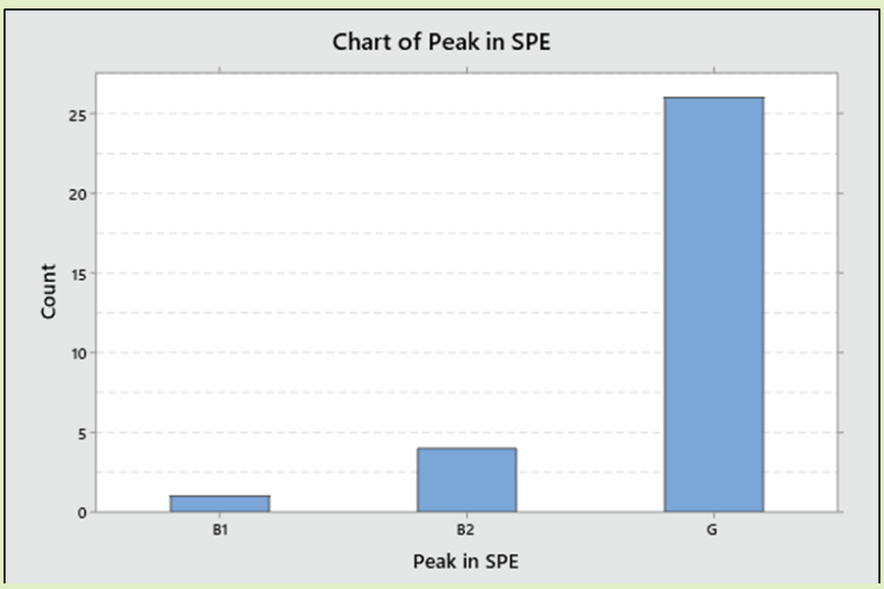


Figure 2: Migration zone of M-band

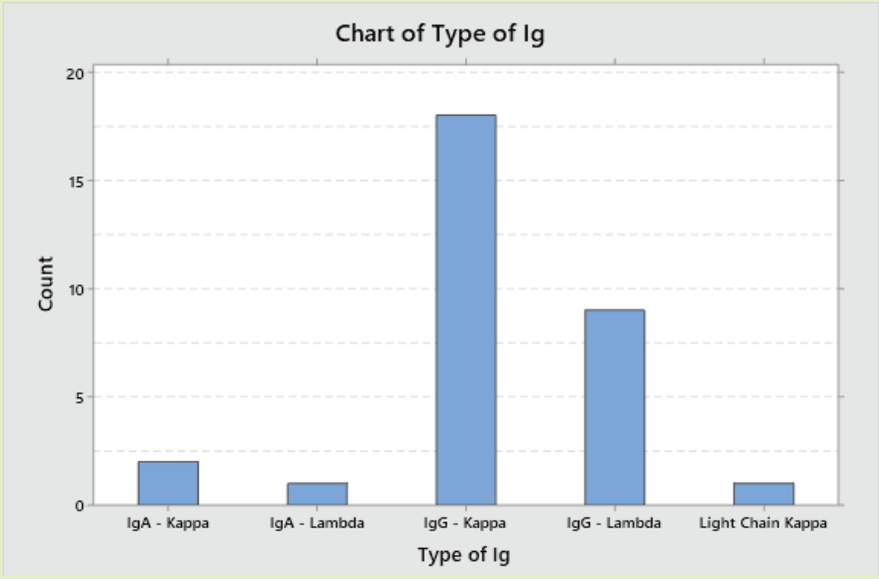


Figure 3: Distribution of Subtype of immunoglobulins

25 patients had abnormal Kappa - Lambda ratio either above or below the reference interval depending on the affected light chain (80.6%) whereas only 8 patients showed involved: uninvolved light chain ratio of >100 (25.8%) and all of them had the involved light chain of >100 mg/L.

An extreme serum free-kappa light chain value of 21564 mg/L which was measured in a patient with IgG-kappa MM, however, had an impact on the calculation of mean and standard deviation.

All our patients had at least one positive CRAB criteria so the utility of involved to uninvolved light chain ratio was minimal in our cohort.

Based on the ISS staging, around 50% of the patients were at stage 3 at the time of diagnosis. (Figure 4)

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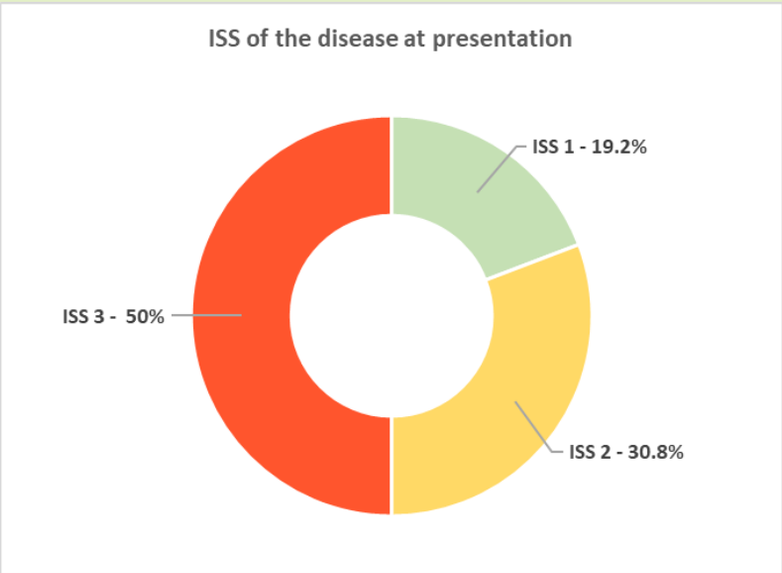

Figure 4: staging of the disease according to ISS at presentation

Conclusions

- The mean age of our patients was 68 with male predominance.
- MM should be one of the differentials in an elderly patient who presents with back pain although it is a non-specific symptom.
- Para-proteins usually migrate to the gamma region, however, migration to beta 2 and beta 1 regions can also be seen.
- Around half of the patients are in the advanced stage at the time of diagnosis so a high degree of clinical suspicion is needed when patients present with non-specific symptoms.
- The given cutoff points of the biochemical biomarkers: albumin-adjusted calcium and creatinine have low sensitivity.
- However, low albumin/globulin ratio, elevated calcium level above the reference range and deranged serum free light chain ratio perform better as a screening mo dality.

Limitations

- The cohort of patients we presented here is at a single tertiary care centre.
- The sample size is low.
- We couldn't include creatinine clearance or eGFR which might be the better indicator than serum creatinine alone.

Acknowledgement

- Dr. Kiran Ghodke - Consultant Haematologist, KDAH, Mumbai, India
- Dr. Nikhil Rabade - Consultant Haematologist, KDAH, Mumbai, India
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A Lady with postmenopausal bleeding

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Case presentation

A 51-year-old lady who was menopause four years back presented with a history of on and off spotting type bleeding for three months. She was reviewed by the gynecology team and had a hysteroscopy which showed some endometrial polyps and the patient also had endometrial hyperplasia. Her endometrial cytology report was normal. The postmenopausal bleeding persists and she was prescribed a course of Norethisterone and around this time she noted hirsutism, abdominal bloating and ankle swelling. She felt more aggressive than earlier but no change in libido. She complained of night sweats with reflux and experienced upper abdominal discomfort with a left sided shoulder pain over last two months. She has no significant family history. Examination was normal except for the presence of hirsutism.

Investigation	Result	Reference Range	Unit
Albumin	32	35 – 50	g/L
Total bilirubin	5	0 – 20	µmol/L
ALP	80	30 -130	U/L
ALT	11	10 -49	U/L
Urine free cortisol	**800**	0 -146	nmol/24 hr
Random cortisol	**1022**	150 – 630	nmol/L
Testosterone by mass spectrometry	**3.5**	0 – 1.8	nmol/L
ACTH	<5	< 50	ng/L
Sodium	137	133 – 146	mmol/L
Potassium	3.5	3.5 – 5.3	mmol/L
Creatinine	46	44 – 97	Qmol/L
CRP	12	0 – 9	mg/L
Magnesium	0.66	0.7 – 1	mmol/L
Plasma Normetadrenaline	< 270	< 1000	pmol/L
Plasma Metadrenaline	< 180	< 600	pmol/L
FSH	**0.9**	23 – 116	U/L
LH	**1.0**	7.9 – 53.8	U/L
Oestradiol	**366**	Up to 118	pmol/L
Hemoglobin	**98**	120 – 156	g/L

Questions

1. What is the next most appropriate investigation?

Answer

1. Urine steroid profile

Results of her 24 hour urine steroid profile is given below.

Steroid	Result (µg/24 h)	Reference Ranges
Androsterone	915	350 - 1190
Aetiocholanoione	809	316 - 1558
DHA	17	83 - 571
11-oxo- Aetiocholanoione	333	178 - 466
11-B-OH Androsterone	**1920**	301 - 753
11-B-OH- Aetiocholanoione	437	177 - 489
Pregnanidiol	66	71 - 1645
Pregnanetriol	222	222 - 668
Androstenetriol	561	60 - 528
Tetrahydrocortisone	**4400**	1158 - 2724
Tetrahydro-11-dehydrocorticosterone	76	130 - 316
Tetrahydrocorticosterone	83	71 - 263
Allo- Tetrahydrocorticosterone	127	107 - 317
Tetrahydrocortisol	**2158**	564 - 1192
Allo-Tetrahydrocortisol	**1087**	294 - 710
α-Cortolone	**1386**	408 - 942
β – Cortolone + β cortol	**1607**	272 - 824
α-Cortol	281	140 - 276
Androsterone + aetiocholanolone	1724	706 - 2708
Total cortisol metabolites	10919	3059 - 6445

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2. What are the abnormalities detected in the urine steroid profile and what is the significance of these results?
3. What is the method and the principle used to separate urine steroid metabolites?
4. What is the next important investigation that helps in diagnosis?
5. What is the most probable diagnosis in this patient?
6. What is the significance of urine steroid profile in this patient?

Answers

2. Very high levels of Tetrahydrocortisone, Tetrahydrocortisol followed by moderate elevation of 11-B-OH Androsterone and mild elevation of Allo-Tetrahydrocortisol, α-Cortolone, β – Cortolone + β cortol noted. Tetrahydrocortisol and tetrahydrocortisone which are the steroid precursor metabolites has a high sensitivity and specificity in detecting adrenal adenoma from carcinoma. Androsterone metabolite also has a good sensitivity and specificity for detecting adrenal carcinoma

3. Gas chromatography mass spectrometry.
The principle is the vaporization of the sample by heat and carried by a carrier gas (Helium/hydrogen) and then the analytes are separated according to the mass/charge ratio by mass spectrometry

4. CT and PET scan - Metabolically active left adrenal mass

5. Adreno cortical carcinoma

6. The serum investigations show an androgen and cortisol excess together with low hemoglobin. Imaging studies helps to come to a diagnosis. But it is not confirmatory. Therefore the urine steroid profile plays a major role in diagnosing patients with Adreno cortical carcinoma. In addition the initial levels of the precursor metabolites helpful to determine the prognosis in patients. After the surgery, during the follow up of this patient urine steroid profile is important to detect tumor recurrences.

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Activities in Brief (2022/2023)
Webinars

Date	Title	Resource persons
24.03.2023	Case Based Approach for Diagnosis of Pleural Diseases	**Dr Amila Rathnapala**, Consultant Respiratory Physician
04.05.2023	Critical Appraisal of a Journal Article	**Prof Tharaka Dassanayake**, Professor in Neurophysiology, Head of the Department of Physiology, Faculty of Medicine, University of Peradeniya
12.05.2023	Evaluation of Liver Biochemistry	**Dr Chathura Lakmal Piyarathna**, Consultant Gastroenterologist and Hepatologist, National Hospital Kandy
28.08.2023	Parenteral Nutrition: Biochemical Monitoring and Metabolic Complications	**Dr Alison Kelly**, Consultant Chemical Pathologist, Glasgow Royal Infirmary, United Kingdom
01.12.2023	Preanalytical and Analytical Pitfalls of the Organic Acid Assay	**Prof Patricia Jones**, Clinical Director, Chemistry and metabolic Disease Laboratories, Children's Health System, Children's Medical Center, Dallas, Texas, United State of America Professor of Pathology, UT Southwestern Medical Center, United State of America
18.12.2023	Guidance to Patients with Raised Triglycerides	**Prof Devaki Nair**, Professor in CVD Prevention and Health Inequality, Consultant in Clinical Biochemistry, Royal Free Hospital, Pond Street, London, United Kingdom

Case Discussions

Date	Title	Resource persons
17.03.2023	A Patient with Hirsutism A Patient with Muscle Weakness A Patient with Cushing Syndrome	Conducted by **Dr B.K.T.P. Dayanath**, Consultant Chemical Pathologist, Colombo North Teaching Hospital **Dr Nadeera Puliyadda** **Dr Medhavi Samarasinghe** **Dr Shanika Halangoda**
19.05.2023	Multifarious Cushing Lesions	Conducted by **Dr Gaya Katulanda**, Consultant Chemical Pathologist, National Hospital of Sri Lanka, Colombo **Dr O.M.O. Siddiqa** **Dr J.E. Liyanagunawardena** **Dr Z.T.M. Thowfeek**
21.04.2023	Vitamins Can Do Magic Mysterious Case of Low Salt	Conducted by **Dr Eresha Jasinge**, Consultant Chemical Pathologist,Lady Ridgeway Hospital for Children, Colombo 08 **Dr Krishanjalee Ranmuthupura** **Dr A Thayani** **Dr Nishani De Silva** **Dr Mihika Fernando**
31.08.2023	A Case Series with Abnormal Parathyroid Hormone Level	Conducted by **Dr Thamara Herath**, Consultant Chemical Pathologist, Medical Research Institute **Dr Jeewanthi Kaushalya** **Dr Nesali Panapitiya**
27.10.2023	Unmasking the Hormonal Maze: Navigating Congenital Adrenal Hyperplasia	Conducted by **Dr Dulani Jayawardana**, Consultant Chemical Pathologist, National Hospital Kandy, and **Dr Jananie Suntharesan**, Consultant Paediatric Endocrinologist, Sirimavo Bandaranayake Specialized Children's Hospital, Peradeniya **Dr Thilini Premadasa** **Dr Hashini Jayasinghe** **Dr Irunika Herath**

Journal Club Presentations

Date	Title	Resource persons
10.08.2023	Original Article; Short-Term and Long-Term Effects of Levetiracetam Monotherapy on Homocysteine Metabolism in Children with Epilepsy: A Prospective Study	**Dr Nuwani Jayasuriya**, Postgraduate Trainee in Chemical Pathology, Lady Ridgeway Hospital for Children (LRH), Colombo 08
07.09.203	Variations in Lipid Profile during Critical Illness	**Dr Dinithi Madurangi**, Postgraduate Trainee in Chemical Pathology, National Cancer Institute, Maharagama
12.10.2023	Original Article; Glycated Albumin for the Diagnosis of Diabetes in IS Adults	**Dr SIddiqa Ozaal**, Registrar in Chemical Pathology, National Hospital of Sri Lanka
23.11.2023	Performance Evaluation of Cardiac Troponin I Assay: A Comparison between the Point-of-care Testing Radiometer AQT90 FLEX and the Central Laboratory Siemens Advia Centaur Analyzer	**Dr Dilini Jayasekara**, Registrar in Chemical Pathology, Colombo North Teaching Hospital, Ragama
21.12.2023	Multiple Cardiac Biomarkers to Improve Prediction of Cardiovascular Events: Findings from the Generation Scotland Scottish Family Health Study	**Dr Nesali Panapitiya**, Registrar in Chemical Pathology, Medical Research Institute

Workshops

On 25th of October, 2023 a workshop on "Navigating Challenge: Empowering Laboratories with Knowledge" was held successfullyat The Grand Leisure Village, Anuradhapura. The target audience was the Medical Laboratory Technologists. Interpretation of EQA Reports, The Pre Analytical Errors – A Continuous Challenge for the Laboratory, Challenges in Body Fluid Analysis, FBC Histograms, Flags and Novel Parameters, Tests of Reproductive Medicine and Biochemistry Auto Analyzer – Is it the Dream of the Lazy Laboratorian, were the lecture topics delivered.

There was a Q and A session which was found extremely helpful by the participants.

On 05th of December, 2023 the same workshop was conducted at The Golden River Hotel, Batticaloa for the Medical Laboratory Technologists in the Eastern province. The lecture topics were Practical Application of IQC, Interpretation of EQA Reports, Answers to the Problems of Immunoassay, Challenges in Body Fluid Analysis, Tests of Reproductive Medicine and Biochemistry Auto Analyzer – Is it the Dream of the Lazy Laboratorian.

This workshop was also found very useful by theparticipants.

CCPSL hopes to conduct similar workshops in remaining provinces in the future.

Collaborative International Symposia

An Internal Symposium on Laboratory Medicine was conducted on 16th September 2023 at Heritance Negombo with the collaboration of IFCC, APFCB and Snibe. The participants were consultant Chemical Pathologists and postgraduate trainees in Chemical Pathology.

For this symposium Dr B.K.T.P. Dayanath (Tacrolimus and Therapeutic Drug Monitoring), Dr Gaya Katulanda (Evidence Based Medicine in the Laboratory Test Selection) and Dr Manjula Dissanayake (Verification of an Examination Procedure) were being the resourced persons form the CCPSL.


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