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Chronic Kidney Disease of Unknown Etiology in Sri Lanka

Pasindu Prabhashana Mayadunna[1], Ghassan Salibi[2], Nikolaos Tzenios[3]
[1] Kursk State Medical. University
[123] Charisma University

Abstract

Background: Chronic Kidney Disease of Unknown Etiology (CKDu) presents a significant health burden in Sri Lanka, particularly in the North Central Province. Despite extensive studies, the etiology remains elusive, making it crucial to investigate the disease's prevalence, risk factors, and impact on the affected populations to formulate effective management and preventive strategies.

Methods and Materials: This cross-sectional survey was conducted in Anuradhapura and Polonnaruwa districts, employing both retrospective data collection from hospital records (2003-2010) and prospective epidemiological and laboratory investigations. The study utilized quantitative and qualitative methodologies, encompassing analysis of medical records, patient surveys, interviews, and laboratory testing for potential etiological factors, including heavy metals and agrochemicals in biological samples.

Results: The study observed a rising incidence of CKDu until 2016, followed by a slight decrease in 2017, possibly attributed to improved drinking water quality. Predominantly affecting males aged 40-60 years, particularly farmers, the five-year survival rate was notably higher in Anuradhapura compared to Polonnaruwa. Geographic clustering of CKDu cases suggested environmental factors, with higher cadmium and fluoride levels in endemic areas pointing towards a complex etiology involving agricultural practices. Despite numerous investigations, no definitive cause has been identified, although the role of environmental and occupational exposures remains a strong hypothesis.

Conclusion: CKDu in Sri Lanka is a multifaceted disease likely influenced by environmental, occupational, and possibly genetic factors. Efforts to improve water quality have shown potential benefits in reducing incidence rates. Future research should focus on comprehensive environmental assessments and targeted interventions to mitigate CKDu risk factors. Establishing national guidelines for management and promoting community awareness are imperative for addressing this public health issue.

Keywords: Chronic Kidney Disease of Unknown Etiology (CKDu), Sri Lanka, Environmental Exposure, Agricultural Practices, Public Health.

Project Definition:

The goal of study on chronic kidney disease is to better understand the illness's causes, risk factors, and course. It also seeks to investigate possible therapies and interventions to enhance patient outcomes and the effects of chronic renal disease on patients' quality of life.

Project Setting:

Two phases of this cross-sectional survey of CKD/CKDu patients were conducted in the districts of Anuradhapura and Polonnaruwa in North Central Province. Using in-ward and clinic patient registers of the medical wards of the North Central Province hospitals from 2003 to 2010 (Anuradhapura district from 2003 to 2010 and Polonnaruwa district from 2006 to 2010), data were first retrospectively retrieved. The hospitals were District General Hospital Polonnaruwa, Base Hospital Madirigiriya, Divisional Hospital Hingurakgoda, and Teaching Hospital Anuradhapura in the Anuradhapura district, and Base Hospitals of Kabethigollawa, Padaviya, and Thambuththegama and Divisional Hospitals of Madawachchiya and Kahatagasdigiliya in the Polonnaruwa district.

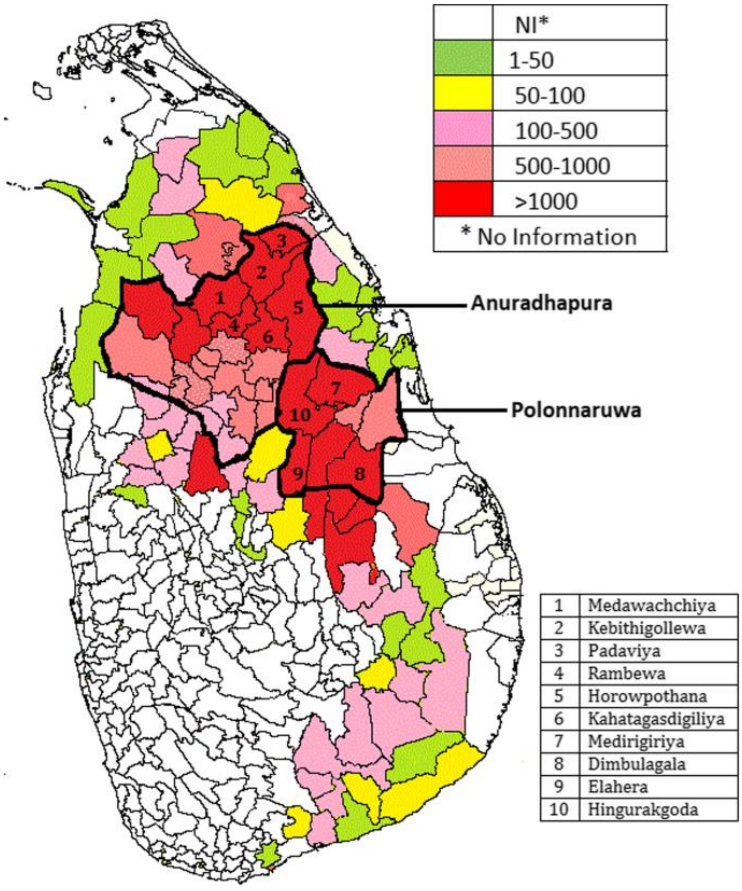

Figure 1 - Total number of CKD/CKDu patients in divisional secretariat areas. The map is created based on the data from this study. (This data was collected from hospitals using the same methodology as in this study from other districts)

Updated Research Summary:

According to my research, North Central Province has an increase in the incidence of CKD/CKDu up until 2016. After 2012, the disease's incidence quickly grew in both districts of

North Central Province. This could have been caused by the health sector's coordinated community-based screening programs, which raised the number of cases detected. Additional considerations include increased exposure to aetiological factors or ones that have not yet been conclusively established. Additionally, this analysis demonstrates that the incidence decreased somewhat in both districts in 2017. One likely explanation for this could be the progressively growing availability of clean drinking water in the impacted areas.

In North Central Province, the incidence of CKD/CKDu rose until 2016 and then slightly decreased in 2017. The availability of clean drinking water could explain this. The 40- to 60-year-old age range is the most susceptible. The majority is made up of men. It appears that farmers are more vulnerable. Most patients, according to the scant data, are in stage 1 of CKD 71.2% was the five-year survival rate. Compared to Polonnaruwa district (5 years survival rate 68.3), Anuradhapura district (5 years survival rate 72.4) has a substantially greater survival rate. Among the CKD/CKDu patient deaths Within the first year of diagnosis, 1685 (17.5% of all CKD/CKDu patients, or 67.6% of all CKD/CKDu patient deaths) happened, whereas 578 (6% of all CKD/CKDu patients, or 23.2% of all CKD/CKDu patient deaths) occurred within the first three years after diagnosis. Twenty-six3 people passed away within the first five years of diagnosis (representing 21.4% of all CKD/CKDu patients and 82.8% of all CKD/CKDu patient deaths).

A higher incidence of CKD/CKDu is seen in clusters of areas. According to GPS mapping, geographic clustering is seen even in high-incidence areas. The irrigation tanks and paddy fields were the principal areas where people congregated.

Project Relevance and Rationale:

Objectives:

1. To identify the risk factors linked with the development of chronic renal disease.
2. To evaluate how patients' quality of life is affected by chronic renal disease.
3. To assess the efficacy of the current renal disease treatments for chronic kidney disease.
4. To investigate possible novel approaches to the treatment of chronic renal disease

Methodology:

Both quantitative and qualitative methodologies will be used in the study. Quantitative approaches will analyze patient data from laboratory tests and medical records to find patterns and trends in chronic kidney disease. In order to learn about the lived experience of chronic kidney disease and the difficulties in managing the condition, qualitative methods will be used, including surveys and interviews with patients and medical professionals.

Epidemiological studies:

Research examining the etiology of CKDu has concentrated on pollutants found in drinking water, probable causal agents associated with agricultural activities, and regional distribution based on the prevalence and incidence of CKDu. Human biology research, environmental investigations, and health mapping studies have investigated numerous potential causal agents. The distribution and epidemiology of the illness lead to the hypothesis that it is associated with the environment and presumably has a connection to human activities, particularly agriculture. Although the available information indicates that CKDu is an environmental disease, no clear-cut cause has been found. Geographic distribution and research findings favor a complex etiology.

In comparison to communities without irrigation seepage into wells, those whose drinking water comes from shallow wells near agriculturally developed irrigation systems and where there is evidence of seepage from the irrigation system into the wells are more susceptible to CKDu. Villages that are impacted are frequently found below the water table. On the other hand, populations that are physically adjacent to irrigation systems and get their drinking water from wells supplied by natural springs seem to be less impacted by CKDu. It has been suggested that CKDu is associated with fertilizer runoff from upstream agricultural operations in the hill country and the ensuing ionicity changes that cause a Hofmeister-type protein denaturing nephropathy.

Additionally, it has been discovered that endemic water sources in the impacted areas have noticeably higher fluoride levels. This is because, although having comparable fluoride levels, the drinking water sources in afflicted and unaffected regions have differing ratios of calcium to sodium. In contrast to the 34 to 469 ratio found in non-endemic locations, the Na^+/Ca^{++} ratio in water has been found to be between 1.6 and 6.6 in CKDu regions. High Na^+/Ca^{++} ratios cause fluoride to form complexes with Na^+ in drinking water, which lessens the toxicity of fluoride ions in the body and decreases Ca^{++} absorption. On the other hand, when fluoride is present, greater Ca^{++} levels that result in low Na^+/Ca^{++} ratios exacerbate the damage to tubular cells. However, it is noteworthy that CKDu is not as common in some locations with high fluoride levels; as a result, its toxicity is likely determined by the ratios of Ca^+ to Na^+ ions.

Numerous minerals, metalloids, and metals have been investigated as possible CKDu etiological factors. In Sri Lankan endemic areas, CKDu has been linked to high levels of cadmium and fluoride and intricate connections between the dissolved sodium and calcium ratio in the presence of fluoride. An initial analysis of various heavy metal levels in fish, plants, soil, and water from CKDu-prevalent locations indicated a potential exposure link between elevated environmental cadmium levels and CKDu. The usage of weedicides and fertilizers containing triple super phosphate is the source of cadmium.

It has been demonstrated that the water from multiple tributaries of the Mahaweli River, the main irrigation supply in the impacted areas, has significant amounts of cadmium, far over the advised safe range of 5 ug/L. As a result, cadmium has been thoroughly studied as a potential causal agent in endemic areas, yet research has shown conflicting results. It has been determined by two recent investigations that there is no direct correlation between CKDu and the presence of heavy metal pollutants (such as arsenic [As], cadmium [Cd], lead [Pb], and uranium [U]) in drinking water and urinary excretion of these agents.

In a recent significant study, individuals from endemic locations exhibited urine amounts of discharged glyphosate and heavy metals that exceeded the reference limit. In addition, the creatinine-adjusted values were greater than those of non-endemic patients. The researchers have suggested the synergistic effect of several heavy metals and agrochemicals in this study as a potential mechanism for nephrotoxicity; however, more well-planned experiments are required to investigate this idea further. Overall, there is no solid evidence of a causal relationship between heavy metals and CKDu in any of the epidemiological studies that are currently available.

Laboratory Studies:

Biological specimens from individuals with CKDu have been shown to have higher urine cadmium levels than controls from both afflicted and unaffected areas. In both endemic and non-endemic areas, this community-based cross-sectional investigation revealed that urine cadmium

levels were greater in CKDu patients than in healthy controls; a dose-responsive connection between urinary cadmium concentration and CKDu stage was seen ($p < 0.05$).

Patients diagnosed with chronic kidney disease (CKDu) had a substantially higher mean urine cadmium concentration (1.039 µg/g) than controls from both endemic and non-endemic areas (0.646 µg/g, $p < 0.001$ and 0.345 µg/g, $p < 0.05$), respectively. Additionally, this investigation showed that the levels of lead and arsenic in the urine of both CKDu patients and healthy controls were comparable. Patients with chronic kidney disease (CKDu) had normal quantities of sodium, potassium, calcium, magnesium, copper, zinc, and titanium in their urine. According to the study's findings, exposure to cadmium increases the likelihood of developing CKDu. In contrast to individuals with CKDu, healthy controls had higher amounts of cadmium in their urine in a different investigation, even when urinary creatinine levels were adjusted. This result casts doubt on its causal relationship and raises the possibility that cadmium is only coincidentally related.

A possible correlation between chronic arsenic toxicity and cystic kidney disease (CKDu) has been suggested by a study that analyzed urine and hair samples from both CKDu patients and controls for arsenic. The results showed that 28% of controls and 68% of CKDu patients had urine arsenic levels above the threshold limit of 21 µg/g creatinine for arsenic-related nephropathy. No correlation was found between the consumption of white rice as a staple diet in CKDu cases and matched controls in a study.

In the urine of CKDu patients, pesticides such as 2,4-D, 3,5,6-trichloropyridinol, p-nitrophenol, 1-naphthol, 2-naphthol, glyphosate, and AMPA have been found; however, it is unknown if any of these substances appear to play a causal role in the etiopathogenesis of CKDu. A study carried out in impacted areas when the disease entity was recently established investigated a causal link between CKDu and acetylcholine esterase (AChE) inhibitor pesticides.

Although several theories have been put out, no single agent, heavy metals, minerals, metalloids, mycotoxins, pesticides, or naturally occurring medications has been proven to cause CKDu. Although agricultural regions are geographically associated with them, there isn't enough proof to conclude that any agriculturally related chemical or behavior contributed to the development of CKDu.

Statistical Analysis:

Thirty,566 patients with CKD/CKDu diagnosed at eleven North Central Province hospitals between 2003 and 2017 are included in the study. In Fig. 1, the incidence changes from 2009 to 2017 are displayed individually for the two districts. The incidence of CKD/CKDu increased steadily in both areas between 2009 and 2012. In the districts of Anuradhapura and Polonnaruwa, the increase was from 0.09 to 0.13 and from 0.10 to 0.14, respectively. The frequency increased dramatically between 2013 and 2016, reaching 0.39 in the district of Anuradhapura and 0.46 in Polonnaruwa. However, both districts saw a decrease in the incidence in 2017 (Anuradhapura 0.29 and Polonnaruwa 0.41).

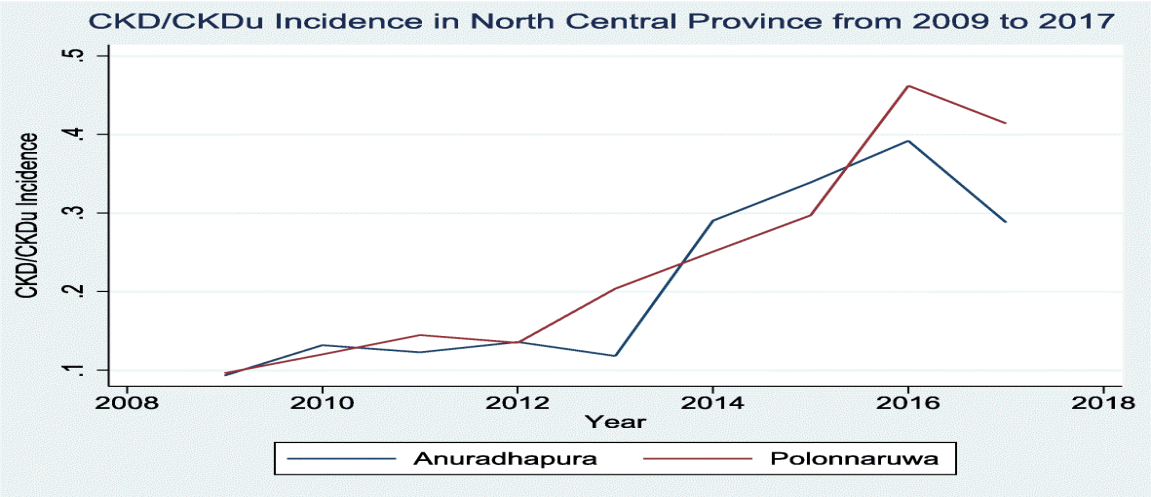

Figure 2 – incidence of CKD/CKDu patients in Anuradhapura and Polonnaruwa districts

In both districts, the male-to-female ratio was higher (1.8:1 in Anuradhapura and 2.2:1 in Polonnaruwa). This male predominance was observed across all age categories and throughout all DS divisions (1.3:1 to 2.6:1). It is highest in the age range of 41–60 years (male: female is 2:1 in Anuradhapura and 2.4:1 in Polonnaruwa) and lowest in the younger age groups (male: female is 1.1:1 in the 11–20 year age group in both districts). The male preponderance decreased after 60 years, although it stayed strong (male-to-female ratios in the >70 years age group was 1.8:1 in Anuradhapura and 2.2:1 in Polonnaruwa).

The most frequently impacted occupational category was farmers (70.6% in the districts of Anuradhapura and 65.1% in Polonnaruwa). Details of the staging (Table 1) were provided only in a fraction of the group (7103, 23.2%). Most CKD/CKDu patients (4943, 69.6%) were in Stage I. There were 2160 (30.4%) patients in Stages II, III, IV, and V, and 547 (7.7%) patients in Stage V. 9653 CKD/CKDu patients were GPS mapped in the 10 DS divisions with the highest incidence, 3318 from Polonnaruwa district and 6335 from Anuradhapura district. In Auradhapura's high-incidence areas, the prevalence of CKD/CKDu ranged from 1.52 to 3.35, but in Polonnaruwa, it was 0.67 to 1.25. In Anuradhapura (72.4, 95% CI 71.10–73.7) and Polonnaruwa (68.3, 95% CI 66.1–70.4), the 5-year survival rate was 71.2. Polonnaruwa district's survival rate is substantially lower than Anuradhapura district's (log-rank test, $p = 0.0212$).

2491 (or 25.8%) of the 9653 patients who had GPS mapping were deceased. Included in this were 1655 deaths (26.1%) from the districts of Anuradhapura and 836 deaths (25.2%) from Polonnaruwa. A total of 1685 deaths (17.5% of all CKD/CKDu patients, or 67.6% of all CKD/CKDu deaths) occurred within the first three years of diagnosis (1115, 67.4% from Anuradhapura and 570, 68.2% from Polonnaruwa districts). Of these deaths, 578 (6% of all CKD/CKDu patients, 23.2% of all deaths in CKD/CKDu patients) occurred within a year of diagnosis (Anuradhapura 396, 23.9%, Polonnaruwa 182, 21.8%).

Twenty-six3 people passed away within the first five years of diagnosis (representing 21.4% of all CKD/CKDu patients and 82.8% of all CKD/CKDu patient deaths). This comprised 701 fatalities (83.9% of all CKD/CKDu patient deaths) from Polonnaruwa districts and 1362 deaths (82.3% of all CKD/CKDu patient deaths) from Anuradhapura. Approximately 2390 patients, or

more than 95% of the total, had no discernible cause of death other than cancer or traffic accidents.

With the exception of GPS mapping, Figure 2 shows the total number of CKD/CKDu patients in the various DS divisions of Sri Lanka that were gathered using the same methods as the current study. The seven DS divisions in the districts of Anuradhapura and Polonnaruwa in the North Central Province are shown in this figure clustered together with CKD/CKDu period incidence of > 2.40. This image also demonstrates the significant number of surrounding districts' contiguous DS divisions.

District	New CKD/CKDu patients 2012–2017 obtained from hospitals				CKD/CKDu cross sectional survey with GPS mapping (from 2012 onwards)					
Anuradhapura	**Male**	**Female**	**Total**	**Period incidence for five year period**	**Number of living CKD/CKDu Patients**	**Total deaths**	**Number of deaths in CKD/CKDu patients (one year period from GPS mapping)**	**Point prevalence of CKD/CKDu**	**Proportion of deaths in CKD/CKDu patients (% for one year period)**	**5 year survival rate**
Madawachchiya	1156	886	2042	4.35	1454	469	81	3.10	5.3	74.6
Padaviya	514	258	772	3.36	770	301	31	3.35	3.9	71.0
Rambewa	530	366	896	2.44	560	234	19	1.52	3.3	70.0
Kahatagasdigiliya	650	426	1076	2.67	678	223	28	1.68	4.0	72.1
Kabethigollawa	424	229	653	2.92	612	167	16	2.74	2.5	76.8
Horowpathana	638	366	1004	2.71	606	261	25	1.64	4.0	67.8
NPC (Nuwaragampalatha Central)	462	220	682	1.11	–	–	–	–	–	–
Maha Wilachchiya	348	157	505	2.25	–	–	–	–	–	–
Galenbindunuwewa	594	314	908	1.93	–	–	–	–	–	–
NPE (Nuwaragampalatha East)	246	136	382	0.55	–	–	–	–	–	–
Nachchaduwa	125	145	270	1.06	–	–	–	–	–	–
Thalawa	453	306	759	1.31	–	–	–	–	–	–
Thirappane	244	319	563	2.08	–	–	–	–	–	–
Nochchiyagama	379	169	548	1.1	–	–	–	–	–	–
Kekirawa	237	151	388	0.65	–	–	–	–	–	–
Palugaswewa	83	48	131	0.84	–	–	–	–	–	–
Mihintale	243	138	381	1.08	–	–	–	–	–	–
Thambuththegama	253	145	398	0.94	–	–	–	–	–	–
Galnewa	215	98	313	0.90	–	–	–	–	–	–
Rajanganaya	209	81	290	0.86	–	–	–	–	–	–
Ipalogama	153	90	243	0.63	–	–	–	–	–	–
Palagala	168	73	241	0.71	–	–	–	–	–	–
Polonnaruwa										
Madirigiriya	1235	591	1826	2.78	820	281	46	1.25	5.3	71.9
Dimbulagala	842	424	1266	1.59	728	267	48	0.91	6.2	64.3
Hingurakgoda	667	443	1110	1.73	639	168	41	0.99	6.0	70.4
Elahera	711	326	1037	2.36	295	120	35	0.67	10.6	63.4
Thamankaduwa	498	274	772	0.94	–	–	–	–	–	–
Lankapura	369	219	588	1.61	–	–	–	–	–	–
Welikanda	376	180	556	1.65	–	–	–	–	–	–

Data obtained from hospitals

Data obtained from cross sectional survey with GPS mapping

Table 1 - Newly reported CKD/CKDu patients and CKD/CKDu prevalence data

Treatment Options:

Medication and pharmacological interventions: Medication is essential when managing kidney disease (CKD). Your healthcare provider may prescribe medicines to control your blood pressure, regulate blood sugar levels, and ease the burden on your kidneys. These medications can significantly slow down the advancement of CKD. Support kidney function. It's important to follow your doctor's instructions and take the medications regularly, even if they don't have a taste, like a tropical getaway.

Dialysis and transplantation: For individuals who have advanced CKD, dialysis or kidney transplantation can be life-saving treatment options. Dialysis helps remove waste products and excess fluid from the blood when the kidneys can no longer do so effectively. On the other hand, kidney transplantation involves replacing a failed kidney with one from a donor. While dialysis and transplantation may seem overwhelming, they have the potential to greatly

enhance your quality of life and provide you with a start. You can think of dialysis as your body's car wash, keeping things clean and functioning smoothly.

Alternative and complementary therapies: Alongside treatments, some people with CKD discover that alternative and complementary therapies provide relief. Practices like acupuncture, herbal remedies, and meditation have been explored to alleviate symptoms and enhance wellness. Nonetheless, consulting your healthcare provider before delving into therapies is crucial. Your doctor can assist you in identifying evidence-based approaches that complement your treatment plan.

Lifestyle Modifications for Managing Chronic Kidney Disease:

Dietary changes and nutritional guidelines: Your diet is crucial for managing CKD. It's important to restrict the intake of nutrients such as sodium, phosphorus, and potassium to maintain the health of your kidneys. Your healthcare provider will likely suggest collaborating with a registered dietitian who can offer tailored recommendations based on your requirements. Remember that although you might crave a bag of chips, your kidneys will greatly appreciate a snack.

Exercise and physical activity recommendations: Regular physical activity and staying engaged in exercise can bring about a range of advantages when managing CKD. Engaging in exercise can contribute to health, the preservation of muscle strength, and weight control. It's crucial to consult your healthcare provider before embarking on any exercise regimen to ensure that it aligns with your health requirements. Rest assured, you don't need to run a marathon to promote kidney health. Smaller manageable activities, like taking a leisurely walk or engaging in light stretching exercises, can make a positive impact.

Managing fluid intake and pressure: It's important to be mindful of how fluid you consume when managing CKD. Your doctor might suggest monitoring and restricting your fluid intake to prevent added pressure on your kidneys. It's also vital to maintain blood pressure because high blood pressure can further harm your kidneys. By following the advice of your healthcare provider regarding fluid intake and blood pressure management, you can stay on the path. Ensure the well-being of your kidneys.

Complications and Long-term Effects of Chronic Kidney Disease:

Cardiovascular complications: Chronic kidney disease doesn't only affect your kidneys. It can also influence aspects of your body, particularly your cardiovascular system. People with CKD have an increased likelihood of developing heart disease, experiencing heart attacks, and suffering from strokes. Collaborating with your healthcare provider to effectively control your blood pressure, cholesterol levels, and other risk factors is crucial to minimize the likelihood of these complications. Keep in mind that a strong and healthy heart is truly beneficial for the well-being of your kidneys.

Anemia, bone disease, and metabolic disorders: Chronic Kidney Disease (CKD) can have complications, including anemia, bone issues, and metabolic disorders. Anemia occurs when the kidneys cannot produce blood cells, leading to feelings of fatigue and weakness. Bone problems can arise due to imbalances in calcium and phosphorus levels, which make the bones weaker and more susceptible to fractures. Additionally, metabolic disorders, like imbalances,

may occur when the kidneys are not functioning optimally. Regular checkups and careful monitoring can help identify and manage these complications.

Effects on mental health and well-being: Living with a long-term condition such as CKD can have an impact on your well-being and overall mental health. The demands of visits, dietary limitations, and the unpredictable nature of the future can feel like a lot to handle. It's essential to prioritize your well-being by reaching out to loved ones for support, considering joining support groups, or even seeking assistance if necessary. Remember that caring for your state is equally vital to caring for your kidneys.

Project Analysis, Evaluation, and Recommendation:

Project analysis: The victims of CKDu, who make up a large portion of the country's CKD burden, are mostly middle-aged or older and come from farming areas in rural Sri Lanka, primarily the North Central Region. Since early disease is asymptomatic, screening can aid in the identification and management of accelerating variables, such as hypertension; these tactics apply to all forms of CKD, and there is currently no particular treatment for CKDu. Advanced renal disease frequently manifests symptoms later in life. After much investigation, the causal agent or agents are still unknown, albeit they seem connected to agriculture and the environment. Whether this is a single-cause entity or a range of nephropathies with overlapping clinic-pathological effects brought on by several causes

Week 2 – I finalized the project purpose, objectives, and design of the project

Week 3-6 – I did analytical studies on my project

Week 7-8 - I arrange meetings with the hospital administrative staff of Anuradhapura and Polonnaruwa district

Week 9 – I arranged a meeting with the nephrology unit of Sri Lanka

Week 10 – discussion with the ministry of education

Week 11-15 - I continue the project

Week 16 – collect feedback and results

Evaluation:

- I was required to collect information from all nephrology units of hospitals in the Anuradhapura and Polonnaruwa districts.
- I was required to collect information from these districts' communities, schools, and educational units.
- I was required to measure the project results by collecting information about chronic kidney disease of unknown etiology in the Anuradhapura and Polonnaruwa districts.

Recommendations:

In order to combat this evolving catastrophe that requires an immediate response, it is important to improve nephrological services and infrastructure in affected areas, develop national guidelines for patients receiving renal replacement therapy in conjunction with individual case management, foster human resource development, promote research, improve social services and train social workers to address issues faced by CKDu patients and their families and ensure streamlined resource management backed by adequate financing.

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