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ORIGINAL PAPER

Risk Attribution for Chronic Kidney Disease of Unknown Etiology (CKDu) with Cyanotoxin Exposure

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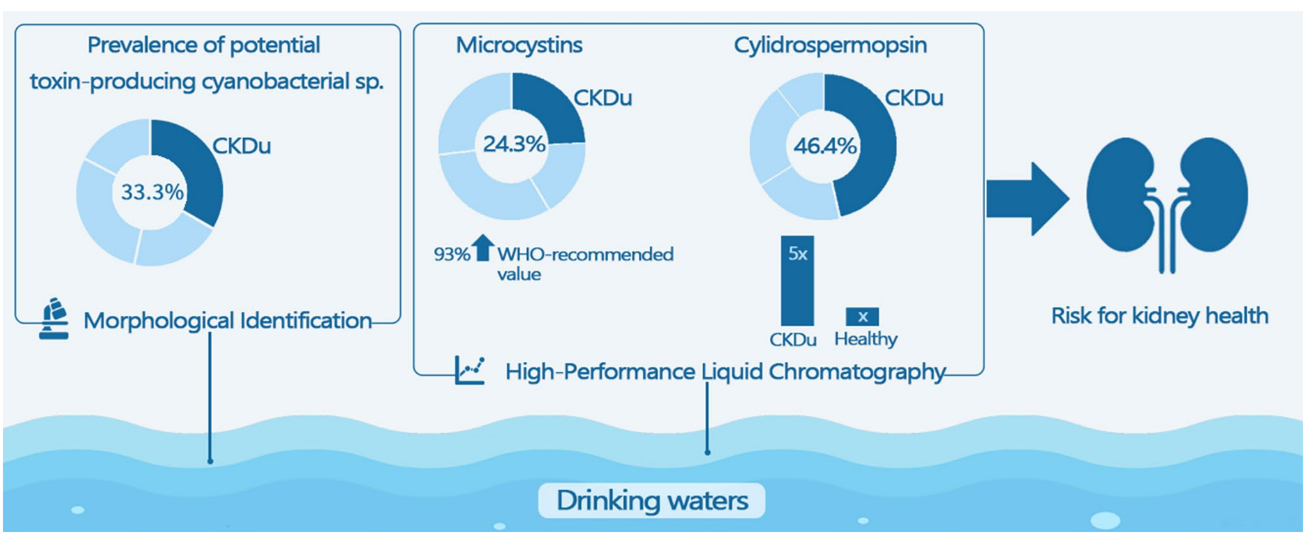
Abstract

The study assessed the cyanotoxin exposure risk for chronic kidney disease of unknown etiology (CKDu) via drinking water, analyzing microcystins (MCs), nodularin (NOD), and cylindrospermopsin (CYN). In two CKDu endemic areas, Girandurukotte and Dehiattakandiya, Sri Lanka, 154 water samples were collected along with 38 from a CKDu non-endemic area, Sewanagala, Sri Lanka. Cyanotoxins were detected using high-performance liquid chromatography (HPLC). MCs were found in 24.3% of CKDu, 17.0% of CKD and 31.7% of Healthy individuals' well waters in the CKDu endemic areas, with 26.8% of Healthy individuals' in the non-endemic area. About 93% of water samples exceeded the World Health Organization (WHO) guideline value for MCs in drinking water (1 µg/L). For CYN, the prevalence was 46.6% of CKDu, 19.6% of CKD, 23.2% of Healthy individuals' in the CKDu endemic areas and 10.7% of Healthy individuals' in the non-endemic area. The CYN mean concentration in CKDu well waters was approximately five-fold higher compared to the non-endemic area (ANOVA, $p = 0.04$). No association was observed between cyanotoxin prevalence in well waters and health status of being CKDu, CKD or Healthy. Most (35.7%) of CKDu individuals exceeded the WHO-recommended tolerable daily intake value (0.03 µg/kg bw/d) for CYN. NOD was not detected in any water sample. Prolonged exposure to MCs and CYN in drinking water may increase stress and weaken the kidneys, rendering it a potential risk factor for CKDu.

Graphical Abstract



Keywords CKDu · Cyanotoxins · Cylindrospermopsin · Groundwater · Microcystins

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Introduction

Cyanobacterial blooms are often hazardous to aquatic organisms, livestock, domestic animals and humans due to their highly toxic secondary metabolites, known as cyanotoxins (Machado et al. 2017; Weralupitiya et al. 2022). The most abundant cyanotoxins in freshwater sources are microcystins (MCs), nodularin (NOD) and cylindrospermopsin (CYN) (He et al. 2022; Manning & Nobles 2017; Weralupitiya et al. 2022). MCs are cyclic heptapeptide hepatotoxins produced by various cyanobacterial genera, including *Anabaena, Cylindrospermopsis, Hapalosiphon, Microcystis, Nostoc* and *Oscillatoria* (Beasley 2020). MCs enclose deleterious effects on human and animal organs, particularly brains, heart, lungs, kidneys and the liver (He et al. 2022; Weralupitiya et al. 2022). Moreover, a study carried out by Piyathilaka et al. (2015) revealed that the viability of human kidney cell lines was significantly decreased due to exposure to microcystin-LR (MC-LR) for 24 h, indicating the potential risk for human kidneys (Piyathilaka et al. 2015). More pieces of evidence to prove the nephrotoxicity of MCs were also reviewed by Xu et al. (2020). NOD, a pentapeptide hepatotoxin, shares structural similarities with MC, and is produced by the cyanobacterial species, *Nodularia spumigena* (Beasley 2020). Even though NOD's toxicity on kidneys is inadequately studied, a case study by Simola et al., (2012) showed renal tubular necrosis in a dog due to exposure to NOD. CYN, a guanidine alkaloid, a hepatotoxin, cytotoxin, and nephrotoxin, is produced by cyanobacterial genera including *Cylindrospermopsis, Dolichospermum, Aphanizomenon, Umezakia, Raphidiopsis, Sphaerospermopsis*, *Lyngbya, Oscillatoria* and *Anabaena* (Diez-Quijada et al. 2022; Moraes et al. 2021; Scarlett et al. 2020; Yang et al. 2021). The toxicity of CYN specially targets the kidneys (WHO 2020b).

Human exposure to cyanotoxins could occur mainly orally by ingesting cyanotoxin-contaminated water or consuming cyanotoxin-contaminated foods and dietary supplements. Further, exposure via bathing, cooking, recreational activities, dermal contact and inhalation are also considered (Codd et al. 2020). Ingestion of large quantities of cyanotoxin-contaminated water or consumption of small amounts for a prolonged time would create a chronic impact (Chorus & Welker 2021). Therefore, provisional guideline values for MC-LR and CYN in drinking water have been established by the World Health Organization (WHO) as 1 and 0.7 µg/L, respectively (WHO 2020a, 2020b). Since the data on NOD are limited, a recommended provisional guideline value has not been implemented. However, scarcity of attention on country-specific standards or legislation to follow WHO guidelines in many developing countries could be a factor in causing acute and chronic diseases related to cyanotoxin exposure.

CKDu is a form of chronic kidney disease which is slowly progressive and asymptomatic kidney failure in the absence of known causative reasons (Pett et al. 2022). In Sri Lanka, CKDu was first reported from the North Central Province (NCP) in the 1990s, and the disease was then spread to several parts of the dry zone of the country, including Uva (Mahiyanganya, Girandurukotte), Eastern (Dehiaththakandiya) and North-Western (Nikawewa) provinces. Even though several causative factors have been hypothesized, the exact cause is still unknown (Hettithanthri et al. 2021). Existing literature on CKDu in Sri Lanka suggests that the disease is likely acquired through environmental factors (Hettithanthri et al. 2021; Rajapakse et al. 2016). Cyanotoxin contamination in freshwaters has raised concerns as a potential causative factor because it is common in CKDu endemic areas and is much higher than in CKDu non-endemic areas in Sri Lanka (Liyanage et al. 2016b; Manage 2019). MCs, CYN, and NOD are the most identified cyanotoxins in CKDu endemic areas (Liyanage et al. 2016a, 2016b; Manage 2019). Research studies have been conducted on the prevalence of cyanobacterial species and cyanotoxins in well waters, reservoirs and irrigation tanks in the dry zone across the country (Imbulana & Oguma 2021; Jayatissa et al. 2006; Magana-Arachchi & Liyanage 2012; Zakeel et al. 2018). Although several studies have examined cyanotoxins in water sources in the dry zone of Sri Lanka, assessing the health risks of consuming cyanotoxin-contaminated water in CKDu endemic areas is crucial. Comparing these risks with CKDu non-endemic areas will help to determine if endemic regions face a higher threat. Therefore, the current study focuses on determining cyanotoxins, including MCs, NOD and CYN in drinking water sources from two CKDu endemic areas in Sri Lanka; Girandurukotte and Dehiattakandiya, and a CKDu non-endemic area in Sri Lanka; Sewanagala, in order to calculate the risk of exposure to cyanotoxins via drinking water. Furthermore, a comparative analysis of socio-demographic information from the particular CKDu endemic areas and non-endemic area was also carried out.

Materials and Methodology

Sampling Locations and Sample Collection

Water samples were collected from two CKDu endemic areas; Girandurukotte area in Uva province, Sri Lanka, during the wet season (February) and the dry season (August) in 2020 and Dehiattakandiya in Eastern province of Sri Lanka during the wet season (April) in 2021. To compare, water samples were also collected from CKDu non-endemic area;

Sewanagala in the Southern province of Sri Lanka, located in the same climatic zone, during the wet season (March) in 2021 and 2022. The sampling locations are shown in Fig. 1. The details of collected water samples are listed in Table 1.

Socio-Demographic Information Collection

Ethical approval for the study was obtained from the Research & Ethics Review Committee of the University

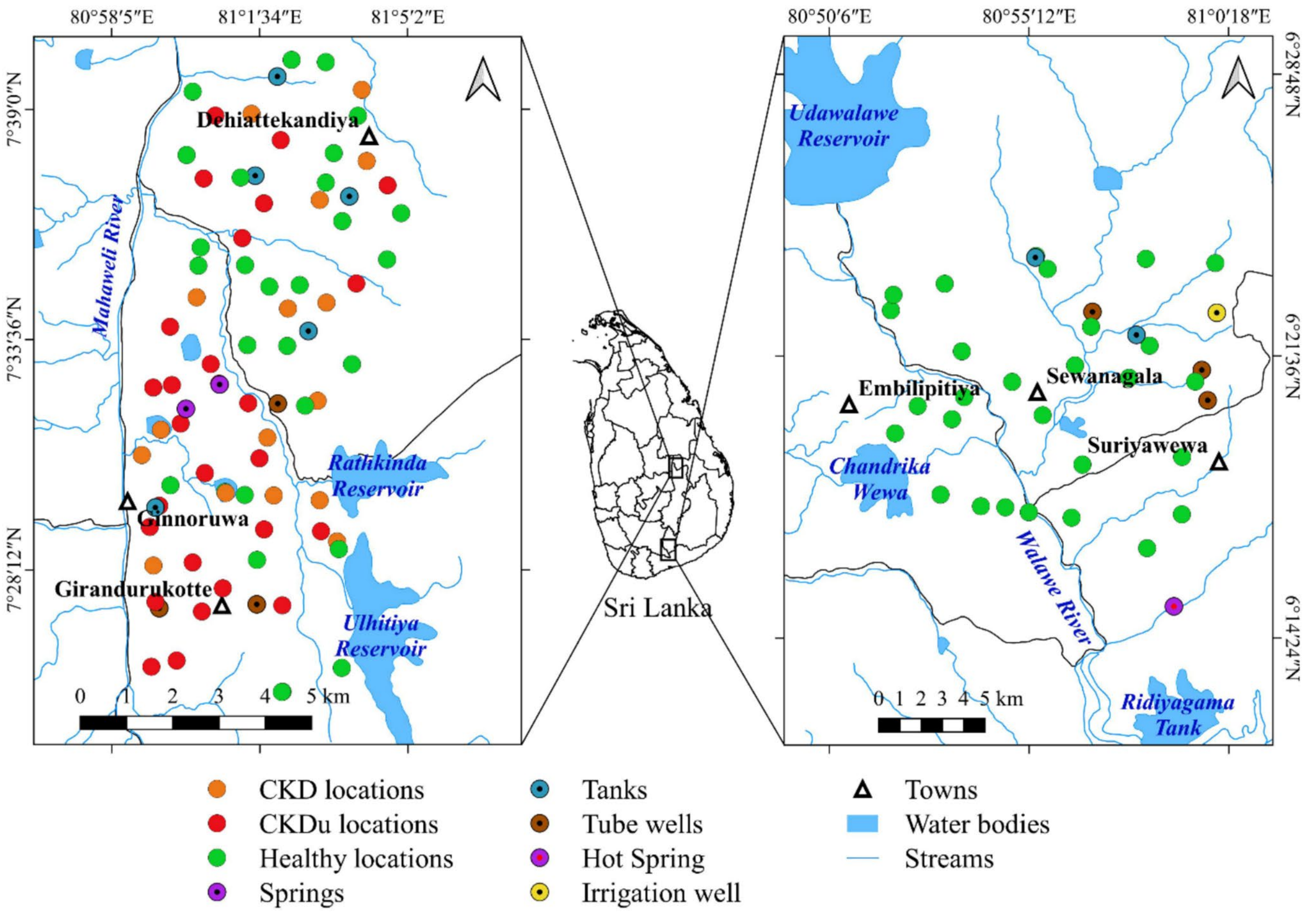

Fig. 1 Sampling locations in CKDu endemic Girandurukotte and Dehiattakandiya and CKDu non-endemic Sewanagala

Table 1 Details of collected water samples

Water samples		Sample numbers			
		CKDu endemic areas			CKDu non-endemic areas
		Girandurukotte wet season	Girandurukotte dry season	Dehiattakandiya wet season	Sewanagala wet season
Dug Wells	CKDu	27	25	10	0
	CKD	9	9	7	0
	Healthy	10	10	20	28
Tube wells		1	3	0	1
Reservoirs		6	2	7	4
Springs		1	2	0	0
Hot springs		0	0	0	1
Water plants		3	1	0	2
Community wells		0	1	0	0
Irrigation wells		0	0	0	2

of Kelaniya, Sri Lanka (UOK/ERC/FS/20/001). Written informed consent was obtained from each participant for their participation. A prepared questionnaire was administered to each participant of CKDu ($n = 25$), CKD ($n = 11$) and Healthy ($n = 8$) from Girandurukotte, CKDu ($n = 11$), CKD ($n = 6$) and Healthy ($n = 18$) from Dehiattakandiya and Healthy ($n = 26$) from Sewanagala to collect socio-demographic information and water usage data including gender, age, occupation, duration of residency in the sampling location, family history of having CKDu, duration lived with CKDu, source of drinking water and daily intake of water. When analyzing the data, Girandurukotte and Dehiattakandiya were considered into "CKDu endemic areas" category with three groups; CKDu, CKD and Healthy (mentioned as Healthy_Endemic). The CKDu non-endemic Sewanagala area was considered as "CKDu non-endemic area" category. The individuals and the water samples from Sewanagala are mentioned as "Healthy_NonEndemic". The people in the Healthy groups were healthy at recruitment with no clinically diagnosed chronic disease.

Culturing and Morphological Identification of Cyanobacteria

Water samples were centrifuged at 3500 rpm for 10 min, and then a mixture of supernatant and the pellet were inoculated into a cyanobacterial-specific BG11 liquid medium. Cultures were incubated at 28 °C under fluorescent light with an intensity of 4.8×10^{-4} cm^{-2}W – 5.9×10^{-4} cm^{-2}W in a 16:8 h D/L cycle for four weeks. The obtained cyanobacterial cultures were observed under the compound light microscope (Olympus BH-2), photographed using cellSens standard imaging software and identified using standard cyanobacterial keys (Abeywickrama et al. 1986; Komárek et al. 2014).

Detection of Cyanotoxins in Water Samples

Extraction and Detection of MCs and NOD in Water Samples

The procedure for MCs extraction from the collected water samples was adapted from Lawton et al. (1994). All reagents were of analytical-reagent or high-performance liquid chromatographic (HPLC) grade. Water samples (250 mL) were filtered through GF/C filter papers which were then cut into small pieces, and shaken with 2.5 mL of 70% methanol for 1 h in the orbital shaker. The re-suspended extract was collected into a glass vial. The procedure was repeated, and the re-suspended extract was combined with the previous. The extract was evaporated in a vacuum oven at 40 °C. Then residue was re-suspended in a 2 mL of 70% methanol + 0.1% TFA. The filtrates were freeze-dried, and the residue was re-suspended in a 2 mL of 70% methanol + 0.1% TFA. Both extracts were filtered through a 0.22 μm syringe filter before HPLC analysis. The total MCs and NOD concentrations in both filter paper and filtrates were determined.

HPLC analysis identified the MCs and NOD concerning the MC standard mixture consisting of MC-RR, MC-YR, MC-LR (SIGMA-ALDRICH 33578) and NOD standard (SIGMA-ALDRICH 32539). HPLC analysis was performed using an Agilent 1260 series HPLC system (Waldbronn, Germany) with diode array-detector at 238 nm and C_{18} column. The column temperature was 40 °C. The injection volume was 20 µL. The mobile phase consists of acetonitrile + 0.05% TFA and ultrapure water + 0.05% TFA. The flow rate was set to 1 mL/min with the following gradient program; a linear gradient series starting with 30% acetonitrile for 10 min, followed by 35% acetonitrile for the next 30 min and to a final eluent condition with 70% acetonitrile for 10 min. The toxin peaks were identified using retention time. Randomly picked samples from both CKDu endemic and non-endemic areas were compared with spikes and blank samples. Furthermore, the concentrations of MCs were determined by calibrating the area under the peak with corresponding standard series.

Extraction and Detection of CYN in Water Samples

CYN extraction was performed using the same procedure as MCs and NOD extraction. HPLC analysis of CYN was conducted according to the protocol described by Welker et al. (2002). The HPLC analysis was performed using the ThermoScientific Ultimate 3000 HPLC system consisting of a C_{18} column. The injection volume was 20 µL. The mobile phase was Mili-Q + 0.05% TFA and 50% methanol + 0.05% TFA. A linear gradient series starting with 100% ultrapure water + 0.05% TFA to a final eluent condition with 0–50% aqueous MeOH + 0.05% TFA after 20 min gave the retention time of 9 min. Peaks were detected at the UV spectrum of 260 nm with the pure CYN standard (SIGMA-ALDRICH 32087). The toxin peak was identified using retention time. Randomly picked samples from both CKDu endemic and non-endemic areas were compared with spikes and blank samples. Furthermore, the concentration of CYN was determined by calibrating the area under the peak with corresponding standard series.

Determination of Human Exposure to Cyanotoxins

Chronic Daily Intake (CDI) values were calculated for total MCs and CYN concentrations found in well water samples, as the majority consumed well water. Each individual, the daily drinking water intake was recorded during the sampling. Since the questionnaire was not administered to children, the daily intake of children was taken as 1 L per day (Xiao et al. 2018). Three age stages were considered for the calculation; children (0–10 years), adolescents (11–19 years) and adults (20–80 years). This calculation only included the individuals who both participated in the questionnaire and had toxins in their well water samples. Equation (1) was used for the calculations (Xiao et al. 2018).

$$\text{CDI}\ (\mu g/\text{kg bw/d}) = \frac{(\text{C} \times \text{IR} \times \text{EF} \times \text{ED})}{(\text{BW} \times \text{AT})} \quad (1)$$

where CDI is chronic daily intake (μg/kg bw/d), C is the concentrations of the cyanotoxins in drinking water (μg/L), IR is the daily intake of drinking water, EF is exposure frequency (d/year), ED is exposure duration (in years: taken from the questionnaire; the duration lived in the particular area at each age stage), BW is the average body weight of children (19 kg), an adolescent (52 kg) and an adult (70 kg), AT is average time (d).

Statistical Analysis

Data from 105 questionnaires were entered using EpiData software. The statistical analysis included descriptive statistics, Chi-square test, and Post hoc pairwise comparisons of the socio-demographic and water usage data using IBM SPSS software (version 25.0). The association between the presence/absence of cyanobacterial genera in well water samples and health status (CKDu, CKD and Healthy_Endemic and Healthy_NonEndemic) was analyzed by Pearson Chi-square test using Origin 2018 software. The association between the presence and absence of MCs and CYN in well water samples and health status (CKDu, CKD and Healthy) was analyzed by Pearson Chi-square test using Origin 2018 software. The total MCs and CYN concentrations in CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic individuals' well water samples were statistically compared using Origin 2018 software (ANOVA, $p < 0.05$).

Results and Discussion

Comparative Analysis of Socio-Demographic Information

CKDu is suggested as a disease that may occur due to environmental risk factors; predominantly affect agricultural communities with limited socio-economic resources (Hewapathirange et al. 2023). The current study aimed to detect potential factors for CKDu, therefore a questionnaire analysis was carried out before any foregone conclusion. According to the results, 83.3% and 64.7% of CKDu and CKD individuals were males, while 73.1% of the Healthy_NonEndemic were also males. (Figure S1). The prevalence of CKDu among males was significantly higher ($p = 0.001$) compared to females in the present study. As per the studies on CKDu prevalence in the world and Sri Lanka, most men involved with agricultural work were more affected than women (Johnson et al. 2019; Lowe & Kumarasinghe 2021; Ruwanpathirana et al. 2019), which showed an agreement with the results of the present study. In the current study, the majority of CKDu individuals were between 46 and 65 years of age. The mean age for CKDu male individuals was 61.6 ± 2.1 years, while 56.6 ± 3.9 years for CKDu female individuals (Table S1). However, no significant difference ($p = 0.375$) was reported in age with the health status (CKDu, CKD and Healthy), but those who were aged over year 55 were more likely to have CKDu. The results on age of the groups agree with the previous studies on CKDu in Central America and CKDu in India, which was more common among men aged 20–50 and 30–60, respectively (Johnson et al. 2019). The occupation of the majority of individuals in the present study was farming, and in comparison with the CKDu non-endemic area (80.8%), more number of individuals from CKDu endemic areas (84.8%) were involved in farming (Figure S2). However, no significant difference was reported between the occupation and the health status ($p = 0.221$). The majority of CKDu (77.8%), CKD (82.4%) and Healthy_Endemic (76.9%) were residents for up to 40 years to date, while 57.5% of Helathy_NonEndemic were residents in the location for up to 40 years (Figure S3). However, the duration of residency in the particular location did not show a significant difference with the health status ($p = 0.287$). When considering only the CKDu group, 77.8% individuals lived 1 to 10 years with the disease CKDu, while the rest (22.2%) lived for more than ten years (Figure S4). As per the results of the study, 44.0% of CKDu individuals have or had CKDu-affected family members, while 17.6% of CKD and 3.8% of Healthy_Endemic individuals have or had CKDu-affected family members. The relationship between the family history of having CKDu and the health status was statistically significant ($p = 0.000$). Interestingly, none from Healthy_NonEndemic individuals' households have or had CKDu-affected family members. The finding could be added as evidence to prove the causative factors for CKDu are within the particular geographical locations.

Previous literature on the socio-demographic analysis of CKDu endemic areas in Sri Lanka provides evidence that the majority considered well water as their primary water source (Gobalarajah et al. 2020; Pett et al. 2022; Ruwanpathirana et al. 2019). Reservoirs and tanks serve as the main water sources for the agricultural purposes in the dry zone of the country. Meanwhile, people depend on ground water sources such as dug wells and tube wells to fulfill their daily necessities (Cooray et al. 2019). According to the socio-demographic analysis of the current study, 61.1% of CKDu individuals used wells as their drinking water source, while its usage was reduced (25.0%) after the diagnosis of

CKDu disease. Apart from wells, prior to the disease CKDu, the CKDu individuals were consuming water from different sources such as agricultural wells, canals and tube wells (Figure S5). Interestingly, before the community water supply was given to the households, the usage of agricultural wells was common among 35.3% of CKDu and 30.6% of CKD individuals while it was not much common in the Healthy_Endemic individuals' (3.8%). The intake of water per day was more than 2 L among 52.8% of CKDu individuals, which reported the highest among the other groups ($p = 0.001$) (Figure S6). Nevertheless, there's a scarcity of the water studies on other different water sources such as irrigation wells and agricultural wells (Pett et al. 2022).

Morphological Identification of Toxin-Producing Cyanobacterial Genera

Cyanobacterial growth could be observed despite the sample location and health status (Table 2). From the total collected well water samples, only 75 samples (48.4%) showed the presence of one or two toxin-producing cyanobacterial genera. Among them, 33.3, 20.0, 29.3 and 17.3% were CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic individuals' well water samples, respectively. No significant difference was reported in the prevalence of toxin-producing cyanobacterial genera among CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic categories (Chi-square, $p = 0.26$). The current study only morphologically identified the cyanobacteria genera present in well waters. Nevertheless, it is recommended to perform molecular identification of cyanobacterial genera of the well waters in the CKDu endemic and non-endemic areas in the dry zone in comparison with the wet zone, and analyze the correlation of the prevalence of cyanobacterial species with CKDu.

Considering the sampling locations, from total well water samples collected from Girandurukotte during the wet season, 23.9, 15.2 and 10.8% of well water samples from CKDu, CKD and Healthy_Endemic individuals showed the growth of one or two toxin-producing cyanobacterial genera. The growth of toxin-producing cyanobacteria such as *Oscillatoria* sp. and *Phormidium* sp. were observed in CKDu, CKD and Healthy_Endemic individuals' well water samples. Apart from the mentioned cyanobacteria, *Microcystis* sp., *Nostoc* sp. and *Pseudoanabaena* sp. growth was observed in CKDu individuals' well water samples. The growth of *Anabaena* sp., *Merismopedia* sp. and *Nostoc* sp. was observed in CKD individuals' well water samples. Furthermore, the Healthy_Endemic individuals' well water samples also

Table 2 Morphologically identified potential MCs, NOD and CYN-producing cyanobacterial genera in collected water samples

		CKDu endemic areas			CKDu non-endemic areas
		Girandurukotte wet season	Girandurukotte dry season	Dehiattakandiya wet season	Sewanagala wet season
Wells	CKDu	*Microcystis* *Nostoc* *Oscillatoria Phormidium* *Pseudoanabaena*	*Fischerella* *Hapalosiphon* *Nostoc* *Oscillatoria* *Phormidium* *Raphidiopsis*	*Anabaena* *Aphanothece* *Oscillatoria* *Phormidium*	–
	CKD	*Anabaena* *Merismopedia* *Nostoc* *Oscillatoria* *Phormidium*	*Oscillatoria*	*Anabaena* *Aphanothece* *Merismopedia* *Oscillatoria* *Phormidium*	–
	Healthy	*Chroococcidiopsis* *Microcystis* *Nodularia* *Oscillatoria* *Phormidium* *Raphidiopsis*	*Nostoc* *Phormidium*	*Anabaena* *Aphanothece* *Microcystis* *Oscillatoria* *Phormidium* *Pseudoanabaena*	*Anabaena* *Chroococcidiopsis* *Leptolyngbya* *Oscillatoria* *Phormidium* *Raphidiopsis*
Tube wells		*Merismopedia* *Oscillatoria*	*Oscillatoria* *Nostoc*	–	–
Reservoirs		*Microcystis* *Nodularia* *Oscillatoria*	*Merismopedia*	*Anabaena* *Oscillatoria* *Phormidium*	*Oscillatoria* *Phormidium*
Water plants (influent)		*Oscillatoria* *Raphidiopsis*	–	*Merismopedia* *Phormidium*	*Phormidium*
Community wells		–	*Anabaena*	–	–
Irrigation wells		–	–	–	*Phormidium*

showed the growth of *Chroococcidiopsis* sp., *Microcystis* sp., *Nodularia* sp., and *Raphidiopsis* sp. *Oscillatoria* sp. was observed in other water samples such as tube wells, reservoir samples, and water plant samples. In addition, *Merismopedia* sp. and *Raphidiopsis* sp. were also observed in tube wells and water plant samples, respectively while *Microcystis* sp. and *Nodularia* sp. were observed in reservoir water samples. Interestingly toxin-producing cyanobacterial growth was observed only in an untreated water sample collected from a water plant, but no cyanobacterial growth was seen in treated water samples.

During the dry season in Girandurukotte, the growth of cyanobacteria, including toxin-producing genera, was observed. The prevalence of toxin-producing cyanobacterial genera was observed in 20.5, 2.27 and 8.81% CKDu, CKD and Healthy_Endemic individuals' well water samples, respectively. The recorded cyanobacterial genera were *Fisherella* sp., *Hapalosiphon* sp., *Nostoc* sp., *Oscillatoria* sp., *Phormidium* sp., and *Raphidiopsis* sp. in CKDu individuals' well water samples. The only toxin-producing cyanobacterial genera observed in CKD well water samples were *Oscillatoria* sp., while the well water samples of Healthy_Endemic showed the growth of *Nostoc* sp. and *Phormidium* sp. The water samples collected from tube wells showed the presence of *Oscillatoria* sp. and *Nostoc* sp. One reservoir water sample showed the growth of *Merismopedia* sp. Further, *Anabaena* sp. was observed in a community well water sample collected from Girandurukotte during the dry season.

Among the well water samples collected from Dehiattakandiya during the wet season, 13.5% CKDu, 18.9% CKD and 37.8% Healthy_Endemic well water samples showed the growth of toxin-producing cyanobacterial genera. The prevalence of *Anabaena sp.*, *Aphanothece* sp., *Oscillatoria* sp., and *Phormidium* sp. were common. Apart from that, one well water sample from CKD showed the growth of *Merismopedia* sp. while two well water samples from Healthy_Endemic showed *Microcystis* sp., and *Pseudoanabaena*. Interestingly, an untreated water sample collected from a water plant showed the growth of *Merismopedia* sp. and *Phormidium* sp.

Well water samples collected from Healthy_NonEndemic individuals, also showed the growth of potential toxin-producing cyanobacterial genera which were common in the water samples from CKDu endemic areas, such as *Anabaena* sp., *Oscillatoria* sp., *Phormidium* sp. and *Raphidiopsis* sp. Furthermore, the two Healthy_NonEndemic well water samples showed the growth of *Chroococcidiopsis* sp. and *Leptolyngbya* sp. The collected water samples from reservoirs showed the prevalence of *Oscillatoria* sp. and *Phormidium* sp. while water samples from water plants and irrigation well water samples showed only the growth of *Phormidium* sp. However, toxin-producing cyanobacterial genera did not originate from the hot spring water sample.

Among the reported toxin-producing cyanobacterial genera, *Anabaena, Aphanothece, Chroococcidiopsis, Fischerella, Hapalosiphon, Merismopedia, Microcystis, Nostoc, Oscillatoria, Phormidium* and *Pseudoanabaena* are known as MCs-producing cyanobacterial genera while *Anabaena, Oscillatoria* and *Raphidiopsis* are known as CYN -producing cyanobacterial genera. Several water samples from CKDu endemic Girandurukotte as well as CKDu non-endemic Sewanagala revealed the prevalence of potential NOD producers such as *Nodularia* sp. and *Leptolyngbya* sp. (Wood et al. 2020).

Morphologically identified, several MCs and CYN-producing cyanobacterial genera in the current study are presented in Fig. 2. In comparison, the prevalence of MCs-producing cyanobacterial genera was higher in well water samples collected from CKDu, CKD and Healthy_Endemic individuals' during the wet season than in the dry season (Fig. 3a). CKDu endemic Dehiattakandiya well water samples showed the highest prevalence of toxin-producing cyanobacterial genera (Fig. 3a, b). However, diversity among the cyanotoxin-producing cyanobacterial genera could be observed in CKDu well water samples compared to other groups (Table 2). The findings in the current study agree with the results of a previous study conducted by Liyanage et al. (2016b), which documented the prevalence of cyanobacterial sp. in CKDu and CKD individuals' well waters in CKDu endemic Girandurukotte (Liyanage et al. 2016b). The study by McDonough et al. (2020), aligns with the findings of the current study as well, indicating the growth of cyanobacterial sp., particularly *Microcystis*, in well water samples in the CKDu endemic Medawachchiya area, Sri Lanka (McDonough et al. 2020).

Detection of Cyanotoxins in Water Samples

Overall, the reported concentrations of total MCs and CYN ranged between Not detected to 65.14 and Not detected to 3.64 µg/L respectively in all water samples from CKDu endemic areas ($n = 154$). They were Not detected to 30.80 and Not detected to 0.93 µg/L in all water samples from CKDu non-endemic area ($n = 38$).

Upon the examination of well water samples ($n = 155$) collected from both CKDu endemic areas and the CKDu non-endemic area, it was reported that 41 samples (26.4%) showed the presence of MCs while 56 samples (36.1%) contained CYN. From the well water samples, which showed the presence of MCs, 24.3, 17.0, 31.7, and 26.8% were CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic samples. Nevertheless, an association between the presence and absence of MCs in well water samples with the status of being CKDu, CKD and Healthy was not observed (Chi-square, $p = 0.08$). In the case of well water samples indicating the presence of CYN, 46.4, 19.6, 23.2 and 10.7% were

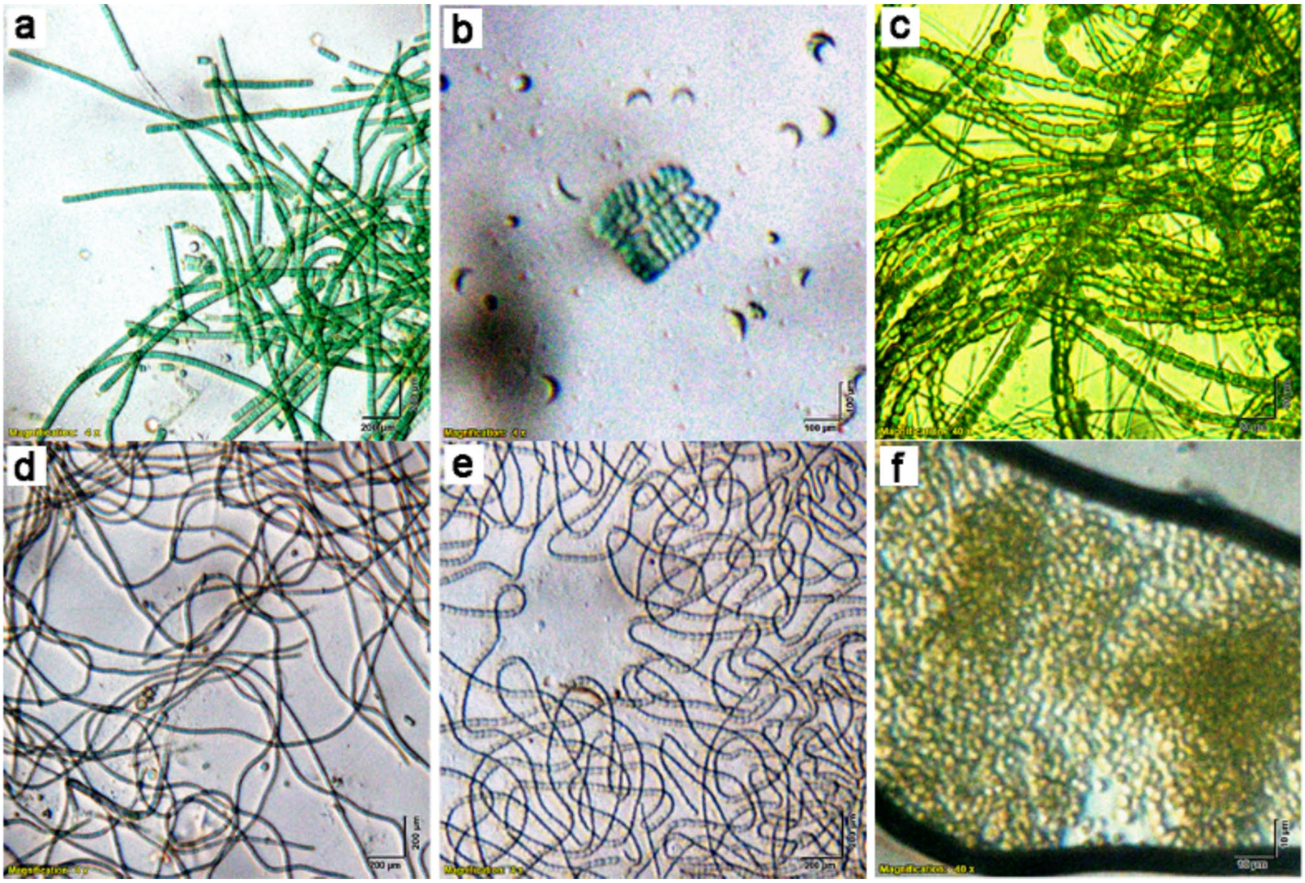

Fig. 2 Morphology of identified toxin-producing cyanobacterial genera **a** *Oscillatoria* sp. **b** *Merismopedia* sp. **c** *Anabaena* sp. **d** *Phormidium* sp. **e** *Nostoc* sp. **f** *Microcystis* sp

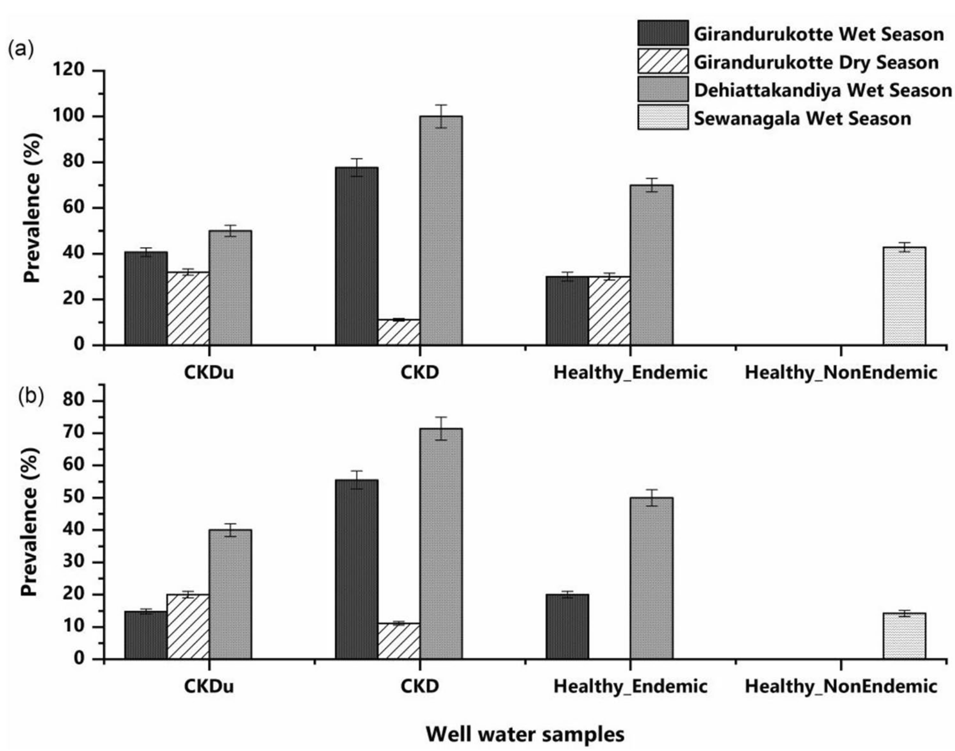

Fig. 3 The prevalence of **a** potential MCs-producing cyanobacterial genera in well water samples **b** The potential CYN-producing cyanobacterial genera in well water samples as a percentage (CKDu: CKDu individuals', CKD: CKD individuals', Healthy_Endemic: Healthy individuals' from CKDu endemic areas, Healthy_NonEndemic: Healthy individuals' from CKDu non-endemic area)

from CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic well water samples. Despite this, no association was observed between the presence or absence of CYN in well water samples and the disease condition of CKDu, CKD, or Healthy (Chi-square, $p = 0.21$).

When the results were arranged according to sampling location and the sampling season, none of the well water samples, the tube well sample, reservoirs water samples, the spring water sample and water plant water samples from CKDu endemic Girandurukotte during the wet season showed the presence of MCs. The reason may be that the concentrations were lower than the detection level of HPLC in the current study.

Nevertheless, the mean concentration of CYN in well water samples collected from CKDu, CKD and Healthy_Endemic individuals in the same sampling location during the same season were 0.0085 ± 0.0040, 0.0028 ± 0.0015 and 0.0014 ± 0.0009 µg/L, respectively. These reported concentrations of CYN in the well water samples from Girandurukotte wet season were below the WHO-recommended provisional guideline value for CYN (drinking water: 0.7 µg/L and recreational exposure: 6 µg/L) (WHO 2020b). Only two out of six reservoir samples from Girandurukotte wet season showed the presence of CYN with concentrations of 0.19 and 0.34 µg/L. Neither the tube well water sample nor the spring water sample showed the presence of CYN. However, two out of three untreated water samples from water plants reported the presence of CYN with concentrations of 0.02 and 0.007 µg/L. These reported concentrations of CYN in the above water samples from the Girandurukotte wet season were below the WHO-recommended provisional guideline value for CYN (drinking water: 0.7 µg/L and recreational exposure: 6 µg/L) (WHO 2020b).

In the same sampling location during the dry season, total MCs in CKDu, CKD and Healthy_Endemic well water samples recorded the mean concentrations of 5.42 ± 2.94, 5.02 ± 2.92, 1.064 ± 1.064 µg/L, respectively. The water sample from the community well revealed a notably elevated value of 98.4 µg/L for total MCs, which drastically exceeded both the WHO-recommended provisional guideline values for MCs in drinking water (1 µg/L) and for recreational exposure (24 µg/L) as well (WHO 2020a). The water sample from the water plant showed the total MCs concentration of 7.76 µg/L. s. Only one out of three tube well water samples showed the presence of total MCs with a high concentration of 11.36 µg/L which exceeded the WHO-recommended provisional guideline value for MCs in drinking water (1 µg/L). None of the water samples from reservoirs and springs from Girandurukotte wet season showed the presence of MCs.

Only two well water samples from CKDu individuals (3.64 µg/L and 0.82 µg/L), in the Girandurukotte dry season exceeded the provisional guideline value for CYN (drinking water: 0.7 µg/L and recreational exposure: 6 µg/L). However, the mean concentrations of CYN in CKDu, CKD and Healthy_Endemic individuals' well water samples were $0.259 \times 10^{-1} \pm 0.145 \times 10^{-1}$, 0.071 ± 0.015 and 0.044 ± 0.009 µg/L. Three out of two tube well samples reported CYN concentrations of 0.03 and 0.30 µg/L. Only one out of the two reservoirs and a spring water sample reported the presence of CYN with concentrations of 0.04 and 0.06 µg/L, respectively. The CYN concentrations of the water sample from the water plant and the community well water sample were 0.35 and 0.08 µg/L. These reported values were below the WHO-recommended value for CYN (drinking water: 0.7 µg/L and recreational exposure: 6 µg/L).

CKDu endemic Dehiattakandiya in wet season recorded the mean concentrations of total MCs in CKDu, CKD and Healthy_Endemic individuals' well water samples as 0.39 ± 0.29, 2.07 ± 0.75, and 1.38 ± 0.32 µg/L, respectively. The mean concentrations of total MCs in CKD and Healthy_Endemic individuals' well water samples exceeded the WHO-recommended provisional guideline value for MCs in drinking water (1 µg/L). Out of the seven reservoir water samples, in six samples, MCs was detected with concentrations of 3.21, 1.61, 1.07, 1.03, 3.59 and 0.98 µg/L which exceeded the WHO-recommended provisional guideline value for MCs in drinking water (1 µg/L).

CYN was detected in one out of ten CKDu individuals' well water samples from Dehiattakandiya in wet season, the reported concentration was 0.008 µg/L. The mean concentration of CYN in Healthy_Endemic individuals' well water samples was 0.0053 ± 0.0040 µg/L. However, the recorded values did not exceed the WHO-recommended provisional guideline value for CYN (drinking water: 0.7 µg/L and recreational exposure: 6 µg/L). CYN has not been detected in CKD well water samples and reservoir water samples.

The control area in the study, Sewanagala, during the wet season, showed the presence of MCs and CYN with mean concentrations of 4.05 ± 1.56 and 0.082 ± 0.0036 µg/L in well water samples. The mean concentration of total MCs exceeded the WHO-recommended provisional guideline value for MCs while the mean concentration of CYN did not surpass the value. The tube well sample collected from Sewanagala during the wet season showed the presence of MCs with concentrations of 19.21 µg/L, which passed the WHO-recommended provisional guideline value for MCs in drinking water (1 µg/L). Among the four reservoir samples, only one showed the presence of MC-YR with an elevated concentration of 20.24 µg/L, exceeded the WHO-recommended provisional guideline value for MCs in drinking water (1 µg/L). CYN was not detected in the tube well sample. Both irrigation well water samples reported MCs with 9.25 µg/L and 17.04 µg/L concentrations. The hot spring sample did not show the presence of MCs.

CYN was detected in two out of four reservoir water samples from Sewanagala, with concentrations of 0.03 and 0.01 μg/L. The hot spring sample did not show CYN.

The mean concentrations of MCs and CYN in well water samples from both CKDu endemic areas and the non-endemic area are summarized in Table 3. However, the cyanotoxin: NOD was not detected in any of the tested water samples even though possible nodularin-producing cyanobacterial genera were morphologically identified. The reason may be due to the concentration of the NOD in the water samples being lower than the detectable levels of the current study. When considering only the well water samples from CKDu endemic areas and the CKDu non-endemic area, the mean concentration of total MCs in well water samples varies as Healthy_NonEndemic > CKD > CKDu > Healthy_Endemic (Fig. 4a). No significant difference was observed in total MCs concentration among CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic well water sample groups (ANOVA, $p > 0.05$). The mean CYN concentrations vary as CKDu > CKD > Healthy_Endemic > Healthy_NonEndemic (Fig. 4b). Interestingly, the mean concentration of CYN in CKDu well water samples was significantly higher than that of Healthy_NonEndemic (ANOVA, $p = 0.04$) well water samples. However, there are a limited number of previous studies which reported the concentration of CYN in water sources in Sri Lanka. The study done by Liyanage et al. 2013 reported mean CYN concentration in Jaya ganga, Kala wewa, Nuwara wewa and Tissa wewa in CKDu endemic Anuradhapura area in the dry zone, as 0.104, 0.091, 0.255 and 0.0967 ng/ml, respectively (Liyanage et al. 2013). The study by Abeysiri et al. 2018 reported mean concentrations of CYN in CKDu individuals' well waters in CKDu endemic Medirigiriya area in the dry zone, were between 0.38 ± 0.01 μg/L to 1.45 ± 0.08 μg/L and

Table 3 Mean concentrations of total MCs and CYN in well water samples from the CKDu endemic areas and non-endemic area

Mean concentrations ± SE of total MCs and CYN (μg/L) in well water samples								
	CKDu endemic areas						CKDu non-endemic area	
	Girandurukotte wet season		Girandurukotte dry season		Dehiattakandiya wet season		Sewanagala wet season	
	MCs	CYN	MCs	CYN	MCs	CYN	MCs	CYN
CKDu	ND	0.0085 ± 0.0040	5.42 ± 2.94	0.259 ± 0.145	0.398 ± 0.29	0.0008 ± 0.0008*	–	–
CKD	ND	0.0028 ± 0.0015	5.02 ± 2.92	0.071 ± 0.015	2.07 ± 0.75	ND	–	–
Healthy	ND	0.0014 ± 0.0009	1.064 ± 1.064*	0.044 ± 0.009	1.38 ± 0.32	0.0053 ± 0.0040	4.05 ± 1.56	0.0082 ± 0.0036

ND: not detected, *detected in only one sample

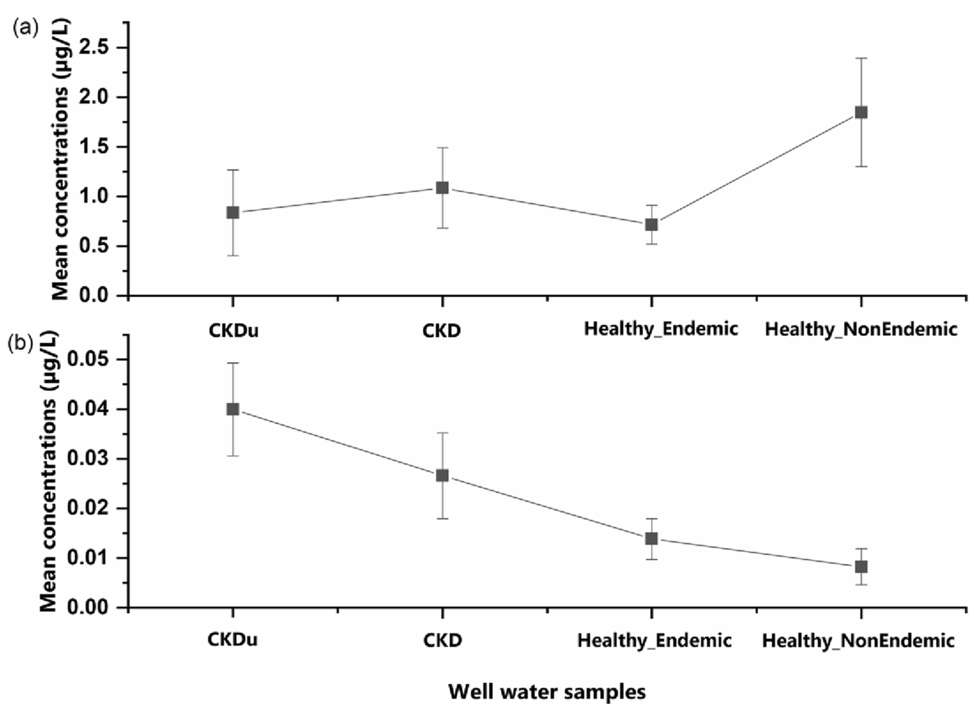

Fig. 4 The comparison of the mean concentrations of **a** total MCs and **b** CYN in well water samples from CKDu endemic areas and non-endemic area (CKDu: CKDu individuals', CKD: CKD individuals', Healthy_Endemic: Healthy individuals' from CKDu endemic areas, Healthy_NonEndemic: Healthy individuals' from CKDu non-endemic area)

0.27 ± 0.04 µg/L to 1.25 ± 0.08 µg/L while the study reported no CYN in the water samples from CKDu non-endemic Hambantota area in the dry zone (Abeysiri et al. 2018). The CYN concentration in the water sources in the wet zone of the country has not been reported in previous literature. However, the study done by Yatigammana and Perera 2017, reported the presence of potential CYN-producing cyanobacterium; *Cylindrospermopsis raciborskii* in Gregory Lake in Nuwara Eliya in the wet zone (Yatigammana & Perera 2017). Jayatissa et al. 2006 analyzed the presence of toxigenic cyanobacterial species in reservoirs from the Dry zone and the wet zone. Nevertheless, the study did not detect CYN-producing cyanobacterial species in the reservoirs in the wet zone (Jayatissa et al. 2006). Therefore, the analysis of CYN concentration and CYN-producing cyanobacteria is crucial. CYN is known as a potential nephrotoxic compound. Since most of the CKDu and CKD individuals' well water samples from CKDu endemic areas contain CYN in the present study, it may damage the already weakening kidneys; when consumed for a prolonged period.

Human Exposure to Cyanotoxins

The results of total Chronic Daily Intake (CDI) (Table S2) reveal that among the population ($n = 39$) exposed to well waters containing MCs, 23.1, 17.9, 30.7 and 28.2% of CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic individuals exceeded the WHO-recommended tolerable daily intake value of MCs (0.04 µg/kg bw/d) (WHO 2020a). Similarly, for CYN, among the population ($n = 42$) who consume from well waters contained CYN, 35.7, 16.6, 11.9 and 9.52% of CKDu, CKD, Healthy_Endemic and Healthy_NonEndemic individuals respectively surpassed the WHO-recommended tolerable daily intake value for CYN (0.03 µg/kg bw/d) (WHO 2020b).

When considering the sampling sites, five CKDu individuals (55.5%), three CKD individuals (33.3%) and one Healthy_Endemic individual (11.1%) from CKDu endemic Girandurukotte population ($n = 9$) exceeded the WHO-recommended tolerable daily intake value of MCs. In the CKDu endemic Dehiattakandiya population ($n = 19$), four CKDu individuals (21.0%), four CKD individuals (21.0%), and eleven Healthy_Endemic individuals (57.9%) exceeded the WHO-recommended tolerable daily intake value of MCs. In the CKDu non-endemic Sewanagala population, all eleven exceeded the recommended value for MCs. Furthermore, in the case of CYN, fifteen CKDu individuals (44.1%), seven CKD individuals (20.5%) and five Healthy_Endemic individuals (14.7%) in the CKDu endemic Girandurukotte population ($n = 34$) exceeded the WHO-recommended tolerable daily intake value of CYN. No individuals' CDI from the CKDu endemic Dehiattakandiya exceeded the recommended value for CYN, while four individuals (66.6%) from CKDu non-endemic Sewanagala ($n = 6$) exceeded it. According to the questionnaire, most individuals with CKDu consume more than 2 L of drinking water and the majority of CKDu individuals have lived in the CKDu endemic area for a long time. Therefore, exposure to these cyanotoxins, especially for CYN via water consumption, could be higher for them than the other groups. However, when considering the other water sources, such as reservoirs, springs, community wells and irrigation wells, the CDI would be higher than in the well waters since the recorded cyanotoxin concentrations were comparatively high. Besides drinking water, it would add an extra exposure risk from cyanotoxins for the residents via recreational activities, cooking, consuming cyanotoxin-contaminated food and other domestic work. Furthermore, the CDI of cyanotoxins via drinking water of an individual may vary depending on the cyanotoxin concentration in water sources during dry and wet seasons (according to the results of the present study). As per the questionnaire, most individuals were farmers, and most CKDu individuals consumed agricultural water before their disease was diagnosed. Therefore, the risk of daily exposure to cyanotoxin-contaminated water is higher in CKDu individuals when compared to other groups.

Conclusion

The socio-demographic analysis of the current study revealed that CKDu is significantly associated ($p < 0.05$) with being a male and CKDu individuals are more likely to have a family history of CKDu. Diversity among the cyanobacterial genera which potentially produce microcystins, nodularin, and cylindrospermopsin, was observed in CKDu well water samples compared to CKD and Healthy well water samples. The mean concentration of total microcystins in CKDu non-endemic Sewanagala well water samples reported the highest while the well water samples from Healthy individuals from CKDu endemic area reported the lowest. However, no significant difference was observed in total microcystins among the well water samples from CKDu, CKD and Healthy individuals'. The mean cylindrospermopsin concentration was significantly higher in CKDu well water samples when compared to CKDu non-endemic Sewanagala well water samples. For cylindrospermopsin, most CKDu individuals exceeded the WHO-recommended tolerable daily intake value (0.03 µg/kg bw/d). Regardless of the sampling location, almost all the water samples exceeded the WHO-recommended provisional guideline value for drinking water (1 µg/L) for microcystins, which reveals a potential risk of weakening the kidneys with chronic exposure. Even though nodularin-producing cyanobacteria genera was morphologically identified in well water samples, the cyanotoxin, nodularin was not detected in any of the tested water samples. Overall, exposure to nephrotoxic cyanotoxins such as microcystins and cylindrospermopsin via drinking water, especially sub-surface water, may increase the health risk to individuals with chronic exposure. The study recommends regular analysis of cyanotoxin content in drinking water and advocates incorporating cyanotoxin assessment, based on WHO guidelines, as a standard parameter in national water quality testing.

Limitations

The study analyzed cyanotoxins in water sources in only one CKDu non-endemic area in Sri Lanka. Future studies on analyzing cyanotoxins, especially microcystins and cylindrospermopsin, in drinking water sources in CKDu non-endemic areas in the dry zone as well as in the wet zone are recommended. The study did not identify toxigenic cyanobacteria in drinking water to the species level. Further studies are recommended to identify the cyanobacterial species in the well water in CKDu endemic areas by molecular identification. The study did not follow the cyanotoxins recovery methods.

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Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sanduni Bandara, Sammani De Silva, Meththika Vithanage and Dhammika Magana-Arachchi. Conceptualization, supervision, project administration reviewing and editing were done by Dhammika Magana-Arachchi, Rasika Wanigathunga, Meththika Vithanage and Anushka Upamali Rajapaksha. The first draft of the manuscript was written by Sanduni Bandara and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval The ethical approval was granted by the Research & Ethics Review Committee of University of Kelaniya, Sri Lanka (UOK/ERC/FS/20/001).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

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