Hypothyroidism among children and adolescents with nephrotic syndrome in Mulago National Referral Hospital, Kampala, Uganda; a cross-sectional study

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Abstract

Background Nephrotic syndrome (NS) is the commonest glomerular disease among children. It is characterized by heavy proteinuria and is a risk factor for hypothyroidism in the affected children. Hypothyroidism is of concern because it affects the physical and intellectual development of children and adolescents. This study sought to establish the prevalence and factors associated with hypothyroidism among children and adolescents with NS.

Methods A cross-sectional design was used to study 70 children and adolescents aged 1–19 years diagnosed with nephrotic syndrome and being followed up in the kidney clinic in Mulago National Referral Hospital. Questionnaires were used to collect patients' socio-demographics and clinical information. A blood sample was taken for analysis for thyroid stimulating hormone (TSH) and free thyroxine (FT4), renal function tests and serum albumin. Hypothyroidism included both overt and subclinical forms. Overt hypothyroidism was defined as TSH level > 10 mU/L and FT4 < 10pmol/L, or FT4 < 10pmol/l with normal TSH, or TSH < 0.5mU/l. Sub-clinical hypothyroidism was defined as TSH ranging between 5 and10 mU/L with normal age appropriate FT4 levels. Urine samples were collected and taken for a dipstick examination. The data was analyzed using STATA version 14. The Bayesian Logistic regression analysis approach was used to estimate odds ratios (OR) and their associated 95% credible intervals. All predictor variables with p value < 0.05 at frequentist statistical analysis were considered significant.

Results The mean age (standard deviation) of participants was 9 years (3.8). There were more males; 36 of 70 (51.4%). The prevalence of hypothyroidism was 23% (16/70 participants). Of the 16 children with hypothyroidism, 3 (18.7%) had overt hypothyroidism while 13 had subclinical hypothyroidism. Only low serum albumin was found to be strongly associated with hypothyroidism; Bayesian OR 132.57 (CI 9.13–567.10) with a frequentist OR of 37 and a p value of 0.001.

Conclusion The prevalence of hypothyroidism among children and adolescent with nephrotic syndrome attending Mulago Hospital paediatric kidney clinic was 23%. Hypoalbuminemia was found to be associated with

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hypothyroidism. Therefore, children and adolescents that have severely low levels of serum albumin should be screened for hypothyroidism and linked to endocrinologists for care.

Keywords Hypothyroidism, Nephrotic syndrome, Hypoalbuminemia, Children, Adolescent

Introduction

Nephrotic syndrome (NS) is one of the most common renal glomerular diseases among children [1]. The incidence of idiopathic NS alone has been reported to be 1.15–16.9 per 100,000 children and this has also been found to vary by ethnicity and region [2]. The disease is classically defined by persistent massive range of proteinuria ($\geq$40 mg/ m^2/hour or urine protein/creatinine ratio $\geq$200 mg/mL or 3+protein on urine dipstick) edema and hypoalbuminemia [3]. NS is a known risk factor for development of hypothyroidism as a result of the disease process and its treatment as well.

NS is characterized by damage to the glomeruli which is responsible for the massive loss of protein in urine. Along with other proteins, thyroxine binding protein (TBG), albumin and thyroxine itself are also lost [4–6]. This causes the free thyroxine hormone (FT4) levels in serum to fall and the anterior pituitary gland attempts to compensate for the loss by releasing thyroid stimulating hormone (TSH). TSH plays the role of stimulating the thyroid gland to produce more thyroid hormones which may still be lost in urine with the on-going nephrosis. TBG and albumin are important carriers of thyroid hormones and act as buffers of serum levels of thyroxine before hypothyroidism eventually occurs [4]. The loss of these two proteins (TBG and serum albumin) in urine affects the serum concentration of thyroid hormones in children with NS [7]. Furthermore, steroids (prednisolone) which are the cornerstone of treatment of NS have also been reported to negatively affect the release of TSH by the pituitary gland and can thus contribute to the development of central hypothyroidism [6]. While higher amounts of serum thyroxine are bound to TBG and serum albumin, the loss of the two carrier proteins in urine among children with NS interferes with the total serum thyroxine level but does not affect the accuracy of serum FT4 in diagnosing hypothyroidism [8]. FT4 measurement can therefore be used as a direct indicator of thyroid function.

Thyroid hormones are important in the normal functioning of physiological systems. Overt hypothyroidism can impair physical growth and intellectual development of children and adolescents if not diagnosed and treated in time [9, 10]. Mario et al. also documented that normalizing the thyroid status of children with NS can improve their response to treatment of the glomerular disease [5]. Despite all this, there is no well-established protocol for screening of children and adolescents with NS for hypothyroidism [6].

Several studies have been conducted in sub-Saharan Africa on the burden of hypothyroidism among special groups of children. However, there remains a paucity of data on the burden of hypothyroidism among the general population of children and adolescents in the region. Galukande et al. conducted a study among young presumably healthy adults attending undergraduate studies at Makerere University in Uganda and found the prevalence of thyroid dysfunction (hyperthyroidism and hypothyroidism) to be at 3.6% [11]. This prevalence was low and can be extrapolated to the general population of children and adolescents living in this same environment with an overall similar diet and socio-economic challenges. In Uganda, proteinuric diseases in children have been reported to be eight times that which is seen in the United Kingdom with an incidence of 160 per a million population per year [12]. There is however, paucity of data on the prevalence of hypothyroidism among children and adolescents with NS in Uganda where a higher incidence of proteinuric diseases are reported. The aim of this study was to therefore establish the prevalence and factors associated with hypothyroidism among children and adolescents with NS.

Methods

Study design and setting

This cross-sectional study was carried out between February 2022 and July 2022 at Mulago national referral hospital (MNRH) children's kidney clinic, in Uganda, East Africa. MNRH is Uganda's largest and oldest national referral hospital and the services in this facility are free except certain laboratory investigations and specialized procedures. It is located in Kampala the capital city of Uganda but the hospital receives patients that are referred from different parts of the country. The paediatrics department has a children's kidney ward where most patients with NS are first admitted before they are later followed up in the outpatient paediatric kidney clinic which runs on Mondays every week, alongside other specialized chronic diseases clinics. The clinic has a total of 100 children and adolescents registered with NS. All their medical information is stored in medical charts kept at the clinic. While NS on the kidney ward and clinic is managed in accordance with the Kidney Disease Improving Global Outcomes [3] guidelines, there is currently no specific guideline or routine screening for hypothyroidism in place. However, growth monitoring is carried out at the clinic.

Study population

All children and adolescents aged 1 to 19 years attending the Paediatric clinic at Mulago hospital with a documented diagnosis of NS in their files at time of enrollment into the clinic that was based on at least two of the following; presence of edema, hypoalbuminemia (≤2.5 g/dl) and proteinuria≥+3 or more on dipstick, irrespective of whether they were in remission or not. Children below 18 years whose caregivers gave written informed consent and those aged 8 to below 18 years who assented were enrolled. Adolescents 18 and 19 years who gave written informed consent were also enrolled. Those that had a prior documented diagnosis of hypothyroidism before NS diagnosis and those that were too sick to withstand the study procedure were not eligible to take part in this study. Information on other factors that could otherwise interfere the thyroid status of the children with NS, for example medication, diet and other underlying medical conditions was collected from the participants but they were not excluded.

Sample size calculation

The sample size was calculated by Leslie Kish formula using a study that was done in Egypt by El-aal et al. with estimated prevalence of hypothyroidism at 23.52% [13].

$$N = (Z\_(\alpha/2)^2 * p(1-p))/\delta^2$$

Where: Z=the standard normal deviate at 5% confidence (1.96).

δ=0.05 the precision or maximum acceptable error to be accommodated, which will be 5%.

P=Estimated prevalence of hypothyroidism among children with NS; 23.52%.

The figure obtained was then adjusted for the number of patients with NS that were already registered in the clinic prior to the commencement of the study. Of the 100 patients registered, 56 had been lost to follow up (had not honored their last appointment for review at the clinic for more than 3 months). It was then assumed 9.8% of those lost to follow up had passed on, according to a meta-analysis by Olowu et al. [14]. The available number of patients was therefore 94.

The sample size was adjusted using the formula;

$$n = N / [1 + \{(N-1)/Pop\}]$$

Where: n=adjusted sample size.

N=the sample size obtained by Leslie Kish formula above (276 participants).

Pop=available population of patients in the clinic (94 patients).

A sample size of 70 participants was obtained.

Study produre

During the study period, 71 patients with a diagnosis of NS attended the paediatric clinic at MNRH and by consecutive sampling, these were screened for eligibility; 70 children and adolescents were enrolled and one was excluded because they declined to provide consent and assent.

An interviewer administered questionnaire was used to collect data on the patient socio-demographics, clinical and NS disease characteristics, other risk factors for hypothyroidism (whether they used iodized salt, history of neck or brain surgeries/irradiations, other chronic medical conditions and medications used). Clinical history suggestive of hypothyroidism was also assessed; history of cold intolerance, constipation, fatigue, weight gain and menstrual irregularities, where applicable. Physical examinations were done and anthropometric measurements including weight in kilograms and length/ height in centimeters that were taken using a weighing scale and stadiometer respectively. The patients' files were reviewed for disease related factors that included the type of NS, cumulative dose of steroids, age at diagnosis of NS and the duration since the diagnosis of NS.

Laboratory investigations

Blood samples were collected in plain red top vacutainers and transported to the laboratory within one hour of sample collection. The laboratory at MNRH was used to carry out the thyroid function tests (FT4, TSH), serum albumin and serum creatinine (from which the estimated glomerular filtration rate, eGFR, was calculated using Schwartz formula) [15]. Thyroid function tests were measured using a fully automated COBAS 6000 ROCHE HITACHI machine from Germany which uses electrogenerated chemiluminescence (ECL) technology in which luminescence is produced during electrochemical reactions in solution and has been reported to be highly specific and sensitive (functional sensitivity at 0.01 mIU/L TSH) [16, 17].

Hypothyroidism in this study included both overt and subclinical forms. Overt hypothyroidism was defined as TSH level>10 mU/L and FT4<10pmol/L or FT4<10pmol/l with normal TSH or TSH<0.5mU/l. Sub-clinical hypothyroidism was defined as TSH ranging between 5 and10 mU/L with normal age appropriate FT4 levels that is: 1-5years [10-23.2pmol/L];6–10 years [10-28pmol/L] and 11–19 years [10-30pmol/L] [18, 19].

Urine samples were collected from each participant and urinalysis was done. Urine protein was categorized as nil, trace, +, 2+, 3+.

Data management

Data was entered into an electronic database using Epidata version 3.1 software package with built-in quality

control checks. It was then exported to Stata version 14.1 (STATA CORP, TEXAS USA for analysis. Frequency and cross tabulations of key variables (background characteristics) such as age, sex, address among others, was done. Frequencies and percentages were displayed in frequency tables. The continuous variables were summarized using means, standard deviations, median and interquartile ranges. The independent variables were each analyzed in respect to the outcome of interest (hypothyroidism) and all predictor variables with P-value<=0.2 were considered for the final model (Bayesian Logistic regression). The Bayesian Logistic regression analysis approach was used to estimate odds ratios (OR) and their associated 95% credible intervals [20]. Credible intervals represented the range of values within which there is a 95% probability that the true predictor variable lies, given the outcome. This approach particularly helped in quantifying uncertainty, especially in this case where the sample size was small. The model was run in respect to the outcome variable of interest (hypothyroidism) with all predictor variables that were statistically significant at

bi-variate and multivariate analysis stage. All predictor variables with p value<0.05 at frequentist statistical analysis were considered significant.

Results

Seventy-one children and adolescents aged 1–19 years were screened during the study period from February 2022 to July 2022 and 70 of these were enrolled. The prevalence of hypothyroidism was 23% (16 of 70 participants) with only 3 of the 16 children having overt hypothyroidism. The study enrollment profile is shown in Fig. 1 below.

Baseline characteristics of patients enrolled

The mean age (standard deviation) of the children and adolescents that were enrolled was 9 years (3.8). The youngest was 2 years old while the oldest was 18 years old. The median age in years at the time of diagnosis of NS for the participants enrolled was 6±3.3 IQR [2–8]. The median (IQR) duration since the diagnosis of NS was made was 15.5 (8–48) months. Thirteen out of 70
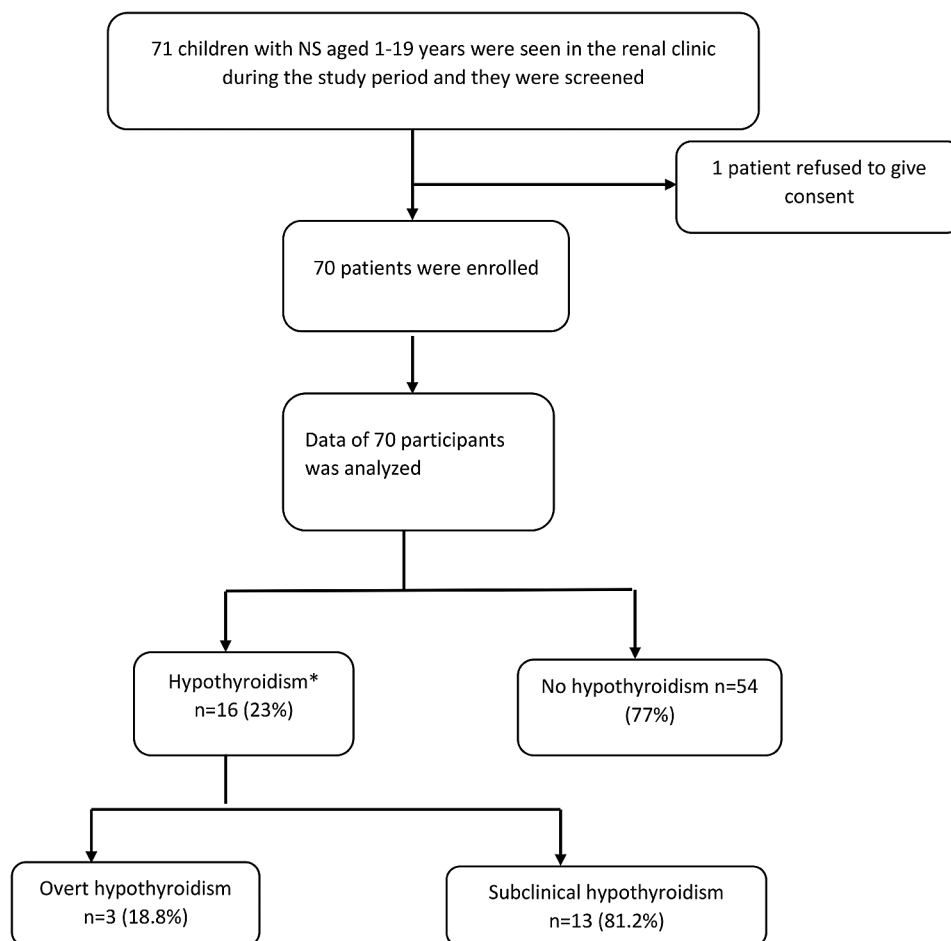
Fig. 1 Study profile of children and adolescents with NS that were enrolled into this study. *those who were found to have hypothyroidism were linked to care in the paediatric endocrinology clinic

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patients (18.6%) resided in mountainous areas. There were 6 out of 70 patients with co-morbidities and these included sickle cell disease (in 3/6), HIV, hepatitis B and tetralogy of fallot. The cumulative dose of steroids was calculated from the patients' records right from the time of enrollment into the renal clinic and the median (IQR) dose was 255.3 (110,490) mg/kg. It was found that

Table 1 Baseline characteristics of children and adolescents with NS that were enrolled in this study

Variable	Frequency (*N* = 70)	Percentage (%)
Age category		
< 5years	11	15.7
5–10 years	31	44.3
> 10 years	28	40
Sex		
Male	36	51.4
Address		
Urban	42	60.0
Type of salt used		
Iodized salt	58	82.9
Local and iodized salt	7	10.0
Local salt	4	5.7
No salt	1	1.4
Weight for Age Z score (≤ 10yrs, n = 41)		
WAZ − 2 to + 2 Z score –Normal	32	78.1
WAZ > + 2 Z score Obese /Overweight[a]	9	21.9
Height for Age Z score		
HAZ ≥ -2 to ≤ + 2-Normal	60	85.7
HAZ < -3 to < -2 –Moderate- severely stunted	10	14.3
Type of nephrotic syndrome		
Steroid sensitive NS	55	67.6.
Steroid resistant NS	11	15.7
Newly diagnosed[b]	4	5.7
Degree of proteinuria on urine dipstick at enrollment		
Nil and Trace	43	61.4
+ 1 and + 2[c]	6	8.6
+ 3 and + 4	21	30
Presence of edema	9	12.9
Medication taken at enrollment		
Prednisolone alone	30	41.1
Prednisolone and other drugs	13	18.8
Other drugs[d]	9	13.0.
None	18	26.1
Laboratory results		
Estimated GFR < 90mL/ min/1.73 m²	7	10.0
Reduced serum albumin (≤ 2.5 g/dL)	17	24.3

[a] None of the children that were overweight/obese had edema

[b] Newly diagnosed were children and adolescents diagnosed in a period of less than 6 weeks and as such could not be classified as SSNS or SRNS

[c] Did not meet nephrotic range proteinuria since they were on treatment

[d] Other drugs included Tenofovir, abacavir, lamuvidine, efavirenz, captopril, folic acid, mycophenolate mofetil, tacrolimus

few patients reported symptoms suggestive of hypothyroidism and none of the children had more than two of the symptoms. Cold intolerance was reported by 11/70 patients (15.7%), 24/70 (34.3%) reported weight gain, 25/70 (35.7%) reported fatigue and 10/70 (14.3%) patients reported constipation. None of the female adolescents reported menstrual irregularities.

Of the patients that took part in the study, 43 out of 70 (61.4%) were in remission (had nil or trace proteins on urine dipstick). Their median serum creatinine levels in mg/dL (normal range 0.3-1 mg/dL) was 0.42(0.3–0.51) and the mean estimated GFR in mL/ min/1.73 m² was 143.4±62.9. The mean serum albumin in g/dL (normal range 3.5–5.5 g/dL) was 3.4±1.2. The median TSH in mU/L (normal range 0.7–4.5 mU/L) was 2.1 IQR (0.9–3.8) while the mean thyroxine level in pmol/L (normal range 10–28 pmol/L) was 15.6±4.1. The rest of the characteristics are shown in Table 1.

Description of the children with NS that had overt hypothyroidism

Three out of 16 participants with hypothyroidism had the overt form. One of these was a 3 year old male who had been first diagnosed with NS at the age of 2 years. He had no symptoms suggestive of hypothyroidism and had a cumulative dose of steroids (prednisolone) of 202 mg/kg. At the time of enrollment into the study he had proteinuria+2 on urine dipstick, serum albumin of 2.0 g/dL and a low FT4 of 7.49 pmol/L.

The second participant was a 4year old female who had been diagnosed with NS 2 months prior to enrollment into the study. She was in remission at the time of enrollment and her prednisolone treatment was being tapered down gradually. Her cumulative dose of prednisolone was 78 mg/kg and she reported to have cold intolerance. Her serum albumin was at 1.26 g/dL and a low FT4 of 5.13 pmol/L.

The third participant was an 11 year old female who had only been diagnosed with NS a month prior to enrollment into the study. She was at Tanner stage I and reported cold intolerance and fatigue. Her cumulative dose of prednisolone was 82.5 mg/kg. She had a proteinuria of +4 on urine dipstick at the time of enrollment into the study, with serum albumin of 1.28 g/dL and a low FT4 of 8.45pmol/L.

Factors independently associated with hypothyroidism

Data collected on the various independent variables was analyzed by the Bayesian logistics regression method and the only factor that was found to be associated with hypothyroidism was reduced serum albumin ≤ 2.5 g/dl. Some of the factors analyzed are presented in Table 2 below.

Table 2 Factors associated with hypothyroidism among children and adolescents with NS using the Bayesian Logistics regression

Predictor Variables	Categories	Bayesian OR(95%CI)	Frequentist OR(SE)	P-value
Serum albumin	Normal	1		
	Reduced	**132.57 (9.13–567.10)**	37.12 (33.69)	**0.001**
Remission status at enrollment	Yes	1		
	No	7.49 (0.48–35.99)	3.56 (3.49)	0.195
Edema at enrollment	Yes	1		
	No	4.18 (0.14–24.54)	1.37 (1.68)	0.795

The texts in bold were the statistical analysis results that were found to be significant; therefore the predictor variable is associated with hypothyroidism

Discussion

This study found a significantly high prevalence of hypothyroidism (23%) among children and adolescents with NS. However, we observed that majority had subclinical hypothyroidism with many being above 10 years of age. This can be explained by the fact that there are various physiological and physical changes that occur in the body of an adolescent that may result in increased secretion of TSH hence predisposing this age group to subclinical hypothyroidism [21]. It is important to note that while subclinical hypothyroidism has been reported to spontaneously resolve in some cases, it can also persist and progress to overt hypothyroidism and hence there is need for continuous monitoring of the affected patients [22].

The prevalence of hypothyroidism found in this study was slightly lower than the 33.3% reported by Marimuthu et al. in a cross-sectional study done in India among children and adolescents aged 1–18 years with NS in the outpatient department [23]. Although Marimuthu's study had participants in a similar age group to this current study, with a mean age of 7.2 years (SD 3.9), the researchers probably reported a slightly higher prevalence because they only enrolled children and adolescents with steroid resistant NS [23]. This type of NS is associated with longer duration of nephrosis therefore they may ultimately be losing more protein and thus loss of T4 and TBG causing hypothyroidism [3]. . In this study however, we enrolled all patients with nephrotic syndrome of which the majority (67.6%, 55 out of 70) had steroid sensitive nephrotic syndrome and as such might be less likely to lose protein (including thyroglobulin, thyroxine and TSH) in urine. It is also important to note that autoimmune thyroid disorders have been reported to be higher in the Asian population and could have perhaps contributed to the high prevalence found by the researchers in the Indian study [24]. Noteworthy, Marimuthu too found a similar proportion of children with subclinical hypothyroidism just like our study despite having a slightly younger population [23]. Therefore subclinical hypothyroidism may be the commonest form of hypothyroidism in NS population and whether this has long term clinical implications for the children and adolescents with NS may need further research through prospective studies.

This study found that patients with a reduced serum albumin were more likely to have hypothyroidism compared to those that had normal levels of the same. The Bayesian OR of 132.7 suggests a substantial positive correlation and the 95% CI ranging from 9.13 to 567.10 implies a high degree of certainty in this association. Furthermore, the frequentist OR of 37.12 is considerably high with also a statistically significant p value of 0.001. Both approaches yielded similar findings hence strengthening the evidence supporting the association between low albumin levels and the risk of hypothyroidism. Children with NS lose protein in urine and among these proteins are thyroglobulin and serum albumin which are important carriers of the thyroid hormones but also the latter which are themselves protein in nature, are lost as well [4]. Serum albumin also acts as a buffer of serum levels of thyroxine before hypothyroidism eventually occurs and once it is lost in urine together with thyroglobulin, the serum concentration of the thyroid hormones also decreases [4]. This explains why the present study found that the children and adolescents that had hypoalbuminemia were more likely to have hypothyroidism. Although, it was not significant in this study, we also noted that majority of the participants with hypothyroidism were not in remission for the Nephrotic syndrome. This would further emphasize that prolonged proteinuria may ultimately lead to hypoalbuminemia with subsequent hypothyroidism.

These findings of hypoalbuminemia being associated with hypothyroidism are similar to the findings in a case-control study by Saffari et al. which was conducted at a paediatric hospital in Qazvin, Iran [25]. The researchers reported a negative correlation between serum albumin and TSH levels in serum. TSH levels increase as a compensatory mechanism to the decrease in serum levels of thyroid hormones resulting from the loss of protein in urine among children and adolescents with NS.

Similarly, El-aal et al. conducted a prospective study at Sohag University Hospital, Egypt over a one-year period among 51 children aged between 1 and 12 years old with NS and found that low levels of thyroid hormones and high levels of TSH (hypothyroidism) was significantly associated with low levels of serum albumin [13].

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While universally most studies have reported a relationship between hypothyroidism and hypoalbuminemia, Jung et al. reported contrary findings in a study conducted at Inje University Busan Paik Hospital, Korea. The researchers enrolled 31 children with NS between January 2001 and December 2017 where they compared their thyroid status during active nephrosis and in remission and they found no significant correlations between serum albumin and T4, TSH, or Free T4 levels [26]. The researchers only found a negative correlation between T3 and serum albumin and they hypothesized that there were probably other mechanisms that could explain this other than the loss of protein in urine. However, the study by Jung et al. had a very small sample size that may not have reached the power to detect the difference between those with low serum albumen and those with normal levels.

Strength and limitations
The study was conducted in the paediatric renal clinic in Uganda's biggest national referral hospital that serves patients from different regions of the country and therefore the findings can be generalized to the rest of the population since there was a fair representation of all the regions of the country. The study also brings new information that shades light on the prevalence and factors associated with hypothyroidism among children with NS in Uganda, East Africa.

However, the study did not exclude autoimmune causes of hypothyroidism among the children with NS that we enrolled. Autoimmune conditions are however not common in the African race and the fact that they were not excluded would likely not alter the findings. In the assessment of thyroid function among the participants in this study, only FT4 and TSH were measured and other tests like serum TBG were not done due to cost limitations. In spite of this, the findings in this study resonate well with those done in other regions which is reassuring that the results are valid [23]. The accessible population of children with NS in this study offered a limited sample size and hence the study may not have adequate power to detect other factors associated with hypothyroidism.

Conclusion
The prevalence of hypothyroidism among children and adolescents with NS in MNRH is quite high as it affects 1 in 4 children. The factor that is associated with hypothyroidism among these children is hypoalbuminemia. Therefore, children and adolescents with NS that have hypoalbuminemia should be screened for hypothyroidism and the treating clinicians should endeavor to achieve and maintain normal albumin levels in these patients. Further studies that are preferably multi-center, with a larger sample size and using a prospective rather than cross-sectional design are recommended. This would better establish a causal relationship between NS and hypothyroidism while a larger sample size allow assessment of more factors that could be associated with hypothyroidism in children and adolescents with NS.

Abbreviations
CI	credible interval
eGFR	estimated glomerular filtration rate
FT4	Free thyroxine
KDIGO	Kidney Disease Improving Global Outcomes
MNRH	Mulago National Referral Hospital
NS	Nephrotic syndrome
SE	Standard error
TSH	Thyroid Stimulating Hormone

Author contributions
All authors contributed equally in carrying out the study and writing the manuscript.

Data availability
The dataset that was generated during this study is not publicly available because we did not obtain consent from all the participants to publish raw data. It can however be availed by the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The School of Medicine Research Ethics Committee of Makerere University (Mak-SOMREC) gave permission to carry out this study; approval reference #Mak-SOMEREC-2021-172. Administrative clearance was obtained from Mulago National referral Hospital ethics committee and the paediatric renal clinic. The caregivers of participants below 18years of age provided written informed consent and all children aged 8-17years provided assent and those 18 and 19 years gave informed consent to participate in the study. All the information collected in this study was treated with uttermost confidentiality and results were only disclosed to the participants, their guardians and clinicians. The participants that were found to have hypothyroidism were linked to the paediatric endocrinology clinic for further medical attention. This research was conducted in line with the declaration of Helsinki guidelines on human subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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