

Subclinical hypothyroidism in CKD patients in a population with a high prevalence of thyroid pathology

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A – Study Design, B – Data Collection, C – Statistical Analysis, D – Data Interpretation, E – Manuscript Preparation, F – Literature Search, G – Funds Collection

Summary Background. Subclinical hypothyroidism (SCH) is established when serum thyroid-stimulating hormone (TSH) is above the defined upper limit and serum free thyroxine (FT4) is within the reference range. SCH is often not detected clinically, and its impact on kidney function is under active consideration, but not well established, despite the fact that hypothyroidism is associated with a negative effect on renal function. SCH may also be associated with low GFR.

Objectives. To evaluate the impact of thyroid dysfunction on renal function in patients with subclinical hypothyroidism.

Material and methods. The study was conducted on the basis of one centre ($n = 1,275$), and the total sample was represented by patients with established CKD. After considering inclusion and exclusion criteria according to the Billewicz scale, determination of creatinine, TSH, T3 and T4 level, as well as estimation of GFR, was performed. Patients were then divided according to their TSH level. The results were analysed using Microsoft Excel, STATISTICA software and MedCalc.

Results. A direct relationship of TSH with creatinine ($\rho = 0.49$; $p < 0.001$) and an inverse relationship with eGFR ($\rho = -0.49$; $p < 0.001$) were found. It was determined that TSH has a good prognostic ability for the prediction of kidney failure (AUC = 0.732; $p < 0.001$), and with a hormone level more than 3.51 $\mu\text{MO/l}$, sensitivity will be 64.44% and specificity – 83.87%.

Conclusions. The negative impact of TSH level on CKD progression already exists, while TSH only decreases to subclinical levels. Thus, SCH could be a significant risk factor for CKD.

Key words: hypothyroidism, glomerular filtration rate, renal insufficiency, chronic.

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Background

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (FT4) within the reference range [1, 2]. SCH cases present with few or no symptoms or signs of thyroid dysfunction, and thus, by its very nature, SCH is a laboratory diagnosis [3]. The prevalence of SCH in the United States in adults is 4–8.5%; moreover, a European study has shown a higher prevalence of SCH among the female population – 10.8% [4]. There is paucity of such data in the Ukrainian population, despite the fact that thyroid pathology ranks first among all endocrinopathies in Ukraine (because of the delayed stochastic effects of the Chernobyl accident), and according to WHO, iodine deficiency – mild to moderate – has also been revealed throughout Ukraine [5]. Thus, there is no accurate data at present on the prevalence of SCH within the territory of Ukraine, but if we compare the prevalence of hypothyroidism in Europe and Ukraine, this is 0.2–2% and 4.1%, respectively [6]. Due to its mostly asymptomatic nature, SCH cases are not detected clinically [2, 3], and its relation to kidney function is also not well established.

Up to now, the association between SCH and the risk of some cardiovascular events has been established, but only in specific subgroups [4, 7]. SCH has been identified as a strong predictor of mortality and a risk factor for cardiovascular disease in patients with chronic kidney disease (CKD) on haemodialysis [4, 8]. However, the association between SCH with the risk of CKD is a matter of debate. The interaction between thyroid and kidney functions is well-known [9]. Thyroid hormones

are involved in the growth, development and physiology of the kidneys [2, 9]. The significant impact of hypothyroidism on biochemical parameters of renal function has been established – in comparison with euthyroidism, the level of serum creatinine is elevated, and glomerular filtration rate (GFR) values are reversibly reduced [2]. SCH also may be associated with low GFR. There is insufficient or no evidence to support an association between SCH and its systemic effects, in particular concerning the impact on renal function [1, 2].

The study was undertaken to evaluate the impact of subclinical hypothyroidism on renal function by estimating serum creatinine and estimated GFR (eGFR) in SCH patients.

Material and methods

With a view to explore the prevalence of thyroid dysfunction, such as SCH, we conducted the single-centre prospective study on the basis of the Centre of Nephrology Care in Dnipropetrovsk Mechnikov Regional Hospital, Dnipro, Ukraine. 1,275 patients were enrolled in our study. They had an established CKD diagnosis and needed the consultation of a nephrologist, according to the family doctor's appointment.

28 individuals taking TH replacement therapy and 145 taking medicines that can interfere with TSH measurement following the European Thyroid Association Guideline: Management of Subclinical Hypothyroidism were excluded [1]. Among the remaining patients, the Billewicz scale was applied (Figure 1) [10]. According to this scale, 981 patients were excluded from the study, because their Billewicz score was < 30 , which precludes both clinical and subclinical hypothyroidism.



	Present	Absent
<u>Symptoms</u>		
Diminished sweating	+6	-2
Dry skin	+3	-6
Cold intolerance	+4	-5
Weight increase	+1	-1
Constipation	+2	-1
Hoarseness	+5	-4
Deafness	+2	0
<u>Signs</u>		
Slow movements	+11	-3
Coarse skin	+7	-7
Cold skin	+3	-2
Periorbital puffiness	+4	-6
Pulse rate	+4	-4
Ankle jerk	+15	-6

A score of +25 or more suggests hypothyroidism, while a score of -30 or less excludes the disease

Figure 1. Billewicz scale

Criteria for inclusion were: established CKD diagnosis; signed informed consent of the patient. Exclusion criteria: patients taking thyroid hormone replacement therapy and drugs that may affect the results of TSH level blood test; type 1 diabetes and type 2 diabetes insulin dependent; body mass index > 40 kg/m²; hemodynamically significant cardiovascular diseases, arrhythmias and heart disease requiring medical or surgical treatment; acute myocardial infarction and acute cerebrovascular accident in up to 6 months; resistant arterial hypertension; severe decompensated heart failure of the III–IV functional class.

In all 121 patients, serum-free triiodothyronine (FT3), serum-free thyroxine (FT4) and thyroid stimulating hormone (TSH) concentrations were measured.

The examined patients were divided into 3 groups of observations depending on the TSH level:

- group 1 (control group) – TSH from 0.27 to 4.0 $\mu\text{MO/l}$ (hormone values within normal range);
- group 2 (main group of observation) – TSH from 4.1 to 10.0 $\mu\text{MO/l}$ (hormone values correspond to subclinical hypothyroidism);

- group 3 (comparison group) – TSH from 10.0 to 25.0 inclusive $\mu\text{MO/l}$ (hormone values correspond to hypothyroidism) (Table 1) (Figure 2).

After reviewing results of the Billewicz scale, 121 patients (12.3%) had signs of thyroid dysfunction, but after performing TSH level analysis – among 53 patients (43.8%), thyroid dysfunction was established: 8 patients (6.6%) with hypothyroidism and 45 (37.2%) with subclinical hypothyroidism. Hence, among all patients: eGFR is the preferred measurement of kidney function in the current study. This is estimated using the CKD-EPI formula.

Significant differences between the groups were found regarding the prevalence of stage 3 CKD in the 2nd group ($p = 0.002$) (Figure 3).

All patients were examined and followed-up according to local and European standards, and all provided informed written consent on data collection. The study was approved by the Ethics Committee at the Dnipropetrovsk Mechnikov Regional Hospital (from 15.11.2016).

Table 1. General characteristics of the study groups

Characteristics	All surveyed	Group 1	Group 2	Group 3	p between groups
Number of patients, n (%)	121 (100.0%)	68 (56.2%)	45 (37.19%)	8 (6.61%)	–
Gender, n (%)					$p = 0.925$
women	97 (80.17%)	55 (80.88%)	36 (80.0%)	6 (75.0%)	
men	24 (19.83%)	13 (19.12%)	9 (20.0%)	2 (25.0%)	
Age, years Me (25%; 75%)	58.0 (48.0; 65.0)	57.5 (46.0; 63.0)	60.0 (50.0; 71.0)	51.5 (47.0; 66.0)	$p = 0.277$
Height, m Me (25%; 75%)	1.66 (1.62; 1.70)	1.66 (1.62; 1.70)	1.66 (1.62; 1.70)	1.65 (1.59; 1.73)	$p = 0.932$
Body weight, kg Me (25%; 75%)	80.0 (69.0; 93.0)	82.0 (69.0; 92.5)	76.0 (68.0; 92.0)	84.0 (79.0; 96.5)	$p = 0.215$
BMI Me (25%; 75%)	29.38 (25.39; 32.89)	29.69 (25.81; 33.40)	27.25 (23.63; 32.05)	30.48 (29.49; 31.27)	$p = 0.182$
Triiodo thyronine, mcg/dl Me (25%; 75%)	4.26 (3.28; 4.78)	4.35 (3.91; 4.8)	3.21 (3.01; 4.59)	3.1 (3.1; 3.5)	$p_{1-2} = 0.212$
Thyroxine, pg/ml Me (25%; 75%)	14.48 (12.44; 17.12)	14.64 (13.14; 17.12)	12.99 (10.97; 17.22)	12.1 (11.18; 13.9)	$p = 0.069$
TSH, $\mu\text{MO/l}$ Me (25%; 75%)	3.54 (1.82; 5.3)	2.1 (1.38; 2.71)	5.3 (4.89; 6.5)	18.21 (13.55; 25)	$p < 0.001$ $p_{1-2} < 0.001$ $p_{1-3} < 0.001$ $p_{2-3} < 0.001$
Daily proteinuria, g/day Me (25%; 75%)	0.23 (0; 1.5)	0.09 (0; 1.5)	0.52 (0; 2.2)	0.18 (0.03; 1.5)	$p = 0.573$

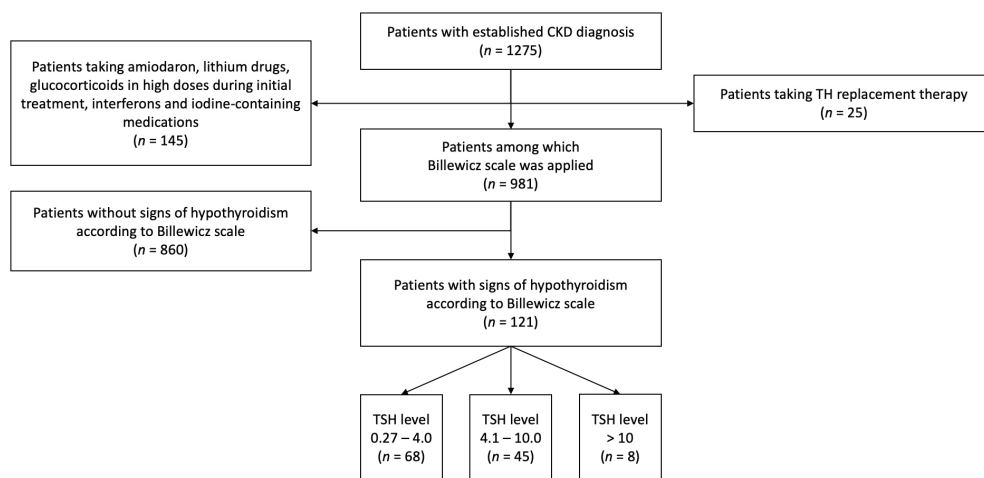


Figure 2. Study design

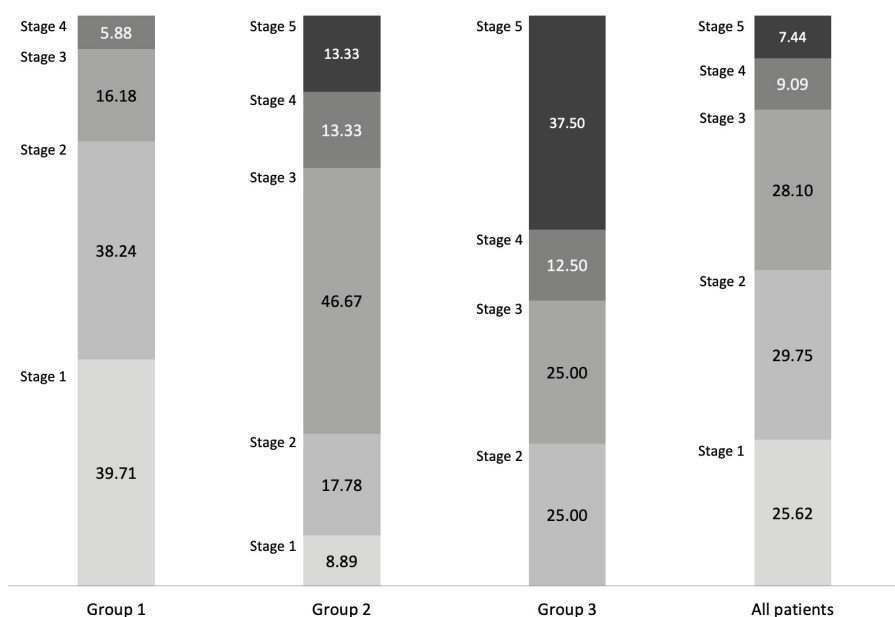


Figure 3. Characteristics of study groups by CKD stages (%)

Statistical methods

Descriptive and analytical biostatistics were used for the statistical processing of the study materials. Median (Me) and interquartile range (25%; 75%) were used to describe the sample abnormal distribution of quantitative traits. Other statistical characteristics were also used: the number of observations (n), relative values (P), 95% confidence interval (CI), the level of statistical significance (p).

The reliability of the difference of means for quantitative traits with abnormal distribution at multiple comparisons was carried out by nonparametric variance analysis. The likelihood of differences in categorical data was estimated by Pearson’s chi-square test (χ^2). Spearman’s rank (ρ) was calculated for correlation analysis. ROC analysis was built on the values of the parameters of sensitivity (Se) and the specificity (SP) test and guidance with 95% CI.

The critical value of statistical significance in the test of null hypotheses was assumed to be 0.05 (5%).

Statistical processing of the results was performed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6. 1 software (StatSoft Inc., Serial No. AGAR909E415822FA). ROC analysis and construction of ROC curves were performed in MedCalc Version 18.2.1, free

trial version (MedCalc Software, Ostend, Belgium; <https://www.medcalc.org/download.php>;2018).

Results

The eGFR differed significantly between study groups ($p < 0.001$) and was highest in group 1, in which it was 81.5 (66.16; 94.64) ml/min/1.73 m², versus 44, 87 (29.81; 60.99) ml/min/1.73 m² in the 2nd group and 28.46 (10.64; 53.18) ml/min/1.73 m² in the 3rd group (Figure 4).

The mean direct correlation was determined between TSH and stages of CKD in the 2nd group of the study, and among all those surveyed, the indicators are, accordingly, $\rho = 0.40$ ($p < 0.001$) for the 2nd group and $\rho = 0.48$ ($p < 0.001$) for all patients.

In all subjects, and in the 2nd group in particular, a direct relationship of TSH with creatinine ($\rho = 0.42$; $p = 0.005$ and $\rho = 0.49$; $p < 0.001$, respectively) and an inverse relationship with eGFR ($\rho = -0.45$; $p = 0.002$ and $\rho = -0.49$; $p < 0.001$, respectively) were revealed (Figures 5, 6).

ROC analysis was performed to evaluate the potential of TSH for the prognosis of chronic renal failure. In order to do this, the examined patients were divided into groups: without renal failure ($n = 39$) and with renal failure ($n = 90$) (Table 2).

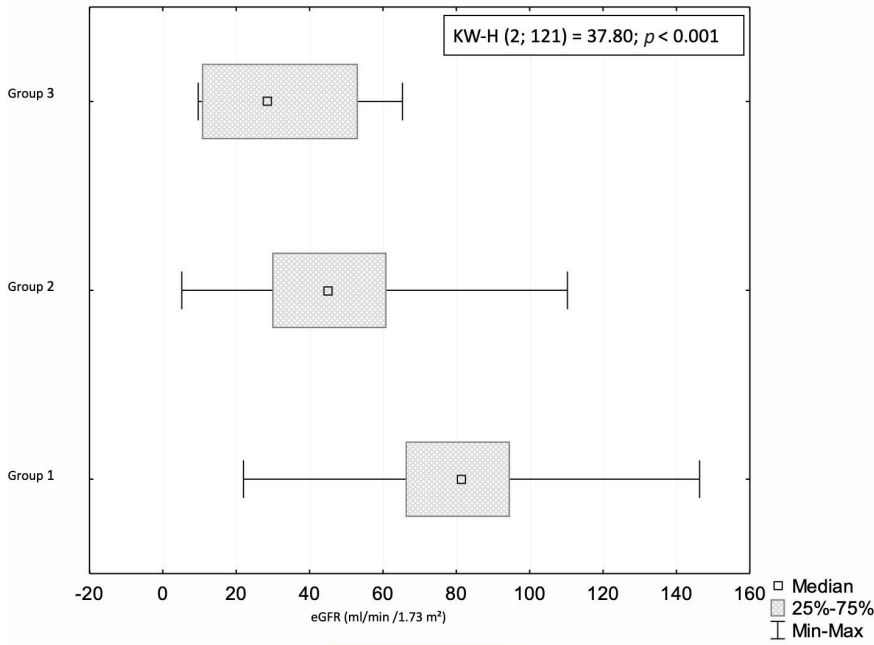


Figure 4. Mean eGFR (ml/min/1.73 m²) in examined patients

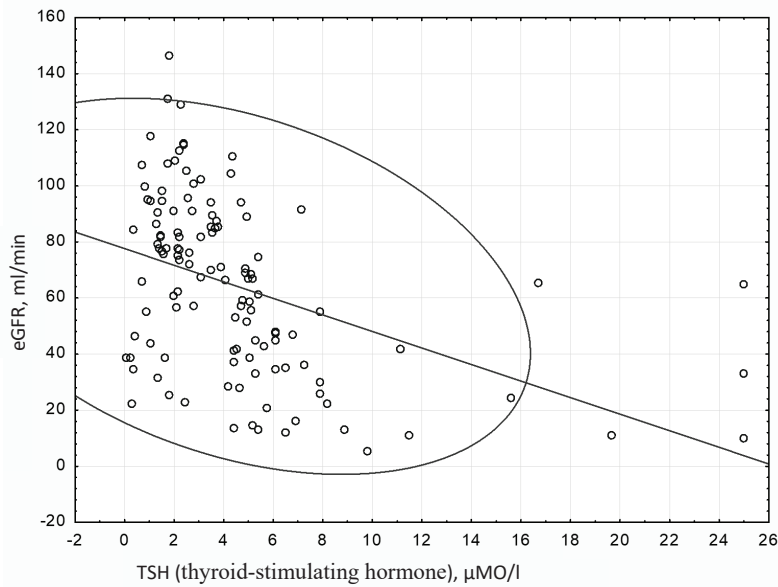


Figure 5. Correlation between TSH level and eGFR among all patients

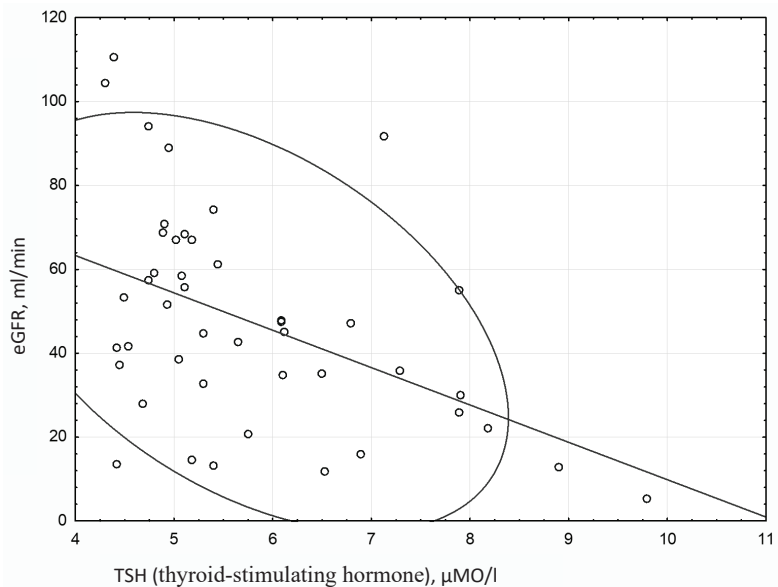


Figure 6. Correlation between TSH level and eGFR in the 2nd group

Table 2. Evaluation of the possibilities of using TSH as prediction of kidney failure (according to ROC analysis)

Indexes	AUC	95% CI AUC	p	Se	Average	Optimal cut-off point
TSH, $\mu\text{MO/L}$	0.732	0.644–0.808	< 0.001	64.44	83.87	> 3.51
Triiodothyronine, ng/ml	0.664	0.453–0.835	0.143	60.00	72.73	> 4.27
Thyroxine, pg/ml	0.643	0.496–0.772	0.075	51.72	81.82	> 15.68
Age, years	0.721	0.629–0.801	< 0.001	50.57	88.46	> 60

AUC – area under curve; Se – sensitivity; Sp – specificity.

The prognostic ability of TSH for the prediction of kidney failure can be estimated as good (AUC = 0.732 ; $p < 0.001$), and with a hormone level more than 3.51 $\mu\text{MO/l}$, sensitivity will be 64.44% and specificity – 83.87% (Figure 7). The prognostic ability of TSH is on the same level as age, which is a proven and significant factor of CKD progression.

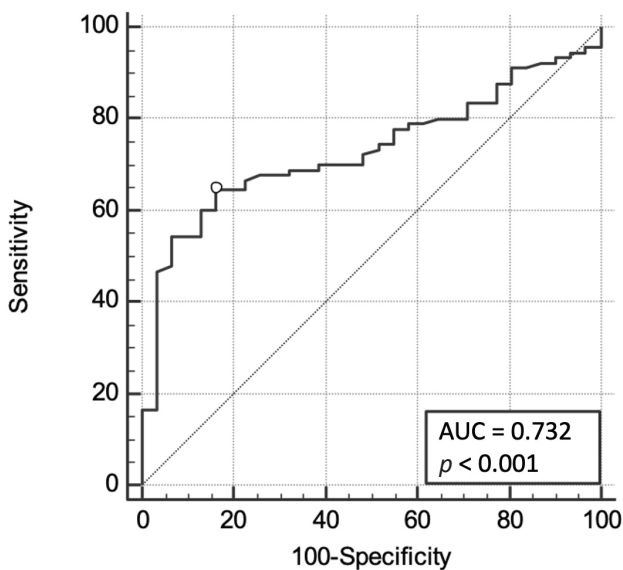


Figure 7. ROC curve for prediction of chronic renal failure based on determination of TSH

Logistic regression analysis showed that the TSH level is a significant independent factor of the development of chronic renal failure. An Odds ratio for TSH – OR = 1.439 (95% CI: 1.099–1.885) shows that with every unit of increase in TSH, the chance of developing renal failure increases by 1.44 times (43.9%).

Discussion

Today, if we are talking about CKD, then such causes as diabetes mellitus and arterial hypertension come first, but the pathology of the thyroid gland also has an effect on the development of this nosology. In particular, this factor may be significant for the Ukrainian region. However, there are no real statistics on the combination of kidney pathology and thyroid dysfunction, which determines the relevance of this study.

The average value of patients with thyroid dysfunction in Europe is 3.7%, while, according to our results, the proportion

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of these patients is 5.4%. Moreover, when we use the Billewicz scale, it increases to 43.8%, i.e. 8.1 times more than the initial ratio. It was also revealed that the percentage of patients with clinical hypothyroidism who, according to recommendations, require TH replacement therapy was 0.8% before using the scale, and after the survey it, was 6.6%, which is 8.25 times higher. Thus, such a simple and available method for examination of patients as the Billewicz scale can significantly reduce the number of patients who require additional laboratory tests in order to determine the degree of functional disorders of the thyroid gland. Thus, the Billewicz scale can be the first step in a diagnostic search at the stage of visiting a general practitioner with a view to avoid excessive laboratory diagnostics.

Our research reported an association between SCH and CKD in hospital-based research. The present evidence suggested that SCH could be a significant risk factor for CKD. There is a linear trend present between TSH elevation and CKD moreover renal failure exists in this study. The exact mechanism by which high serum TSH leads to renal impairment remains unclear, which should prompt future studies.

It is necessary to take into account the fact that our study was conducted on the basis of only one centre, and it would be incorrect to extrapolate the results of this study to the entire population, since this geographical area refers to zones with iodine deficiency, which in turn can affect the prevalence of thyroid pathology.

The study involved patients who were treated in the Centre of Nephrology Care, and the results may possibly change if we add patients with early CKD who are under the supervision of family doctors.

Conclusions

- TSH has direct correlation with stages of CKD in the 2nd group of study and among all those surveyed – $\rho = 0.40$ for the 2nd group and $\rho = 0.48$ for all patients, with creatinine ($\rho = 0.42$; $\rho = 0.49$, respectively), and there is an inverse correlation with eGFR ($\rho = -0.45$; $\rho = -0.49$, respectively). Thus, hypothyroidism without clinical manifestation (TSH up to 10.0 $\mu\text{MO/l}$) can potentiate the progression of CKD. Moreover, patients in this group require more careful monitoring by the family doctor.
- The increase of TSH level is associated with CKD progression: odds ratio for TSH – OR = 1.439 (95% CI: 1.099–1.885); thus, the chance of developing renal failure increases by 1.44 times (43.9%).
- The Billewicz scale could be used by family doctors and internal medicine physicians as an initial survey method for patients with suspected thyroid dysfunction.

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