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The Association of Electrolytes, Trace Elements, and Vitamin C with Kidney Function in Iraqi Celiac Patients

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Abstract

Celiac disease is a chronic autoimmune disorder that occurs in genetically predisposed individuals who consume gluten-containing grains, such as wheat, barley, and rye, triggering a gradual immune response that damages the small intestine and can also affect other organs. Accurate biochemical markers are essential for diagnosis, risk assessment, and the implementation of effective treatments to enhance clinical outcomes. This study aimed to evaluate changes in blood levels of urea, creatinine, electrolytes (sodium, potassium, and chloride), trace elements (magnesium and zinc), and vitamin C in Iraqi individuals diagnosed with celiac disease. A total of 100 patients with celiac disease who were not following a gluten-free diet were compared to 57 healthy controls. The results showed a significant increase in serum urea and creatinine levels ($p < 0.05$), while electrolyte levels remained unchanged. Conversely, trace element levels of (magnesium and zinc), and serum vitamin C levels were significantly decreased in both Patients female (PI) and Patients male (PII) compared to their respective healthy groups control female (CI) and control male (CII). These findings suggest that the observed variations may be linked to an increased risk of renal dysfunction due to elevated serum urea and creatinine levels in individuals with celiac disease.

Keywords: Celiac disease, Anti-tissue transglutaminase antibodies, Electrolyte, Vitamin C, Kidney function.

ارتباط الشوارد والعناصر النزرة وفيتامين سي بوظيفة الكلى لدى مرضى الاضطرابات الهضمية العراقيين

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الخلاصة

مرض الاضطرابات الهضمية هو اضطراب مناعي ذاتي مزمن يحدث لدى الأفراد الذين لديهم استعداد وراثي ويستهلكون الحبوب التي تحتوي على الغلوتين، مثل القمح والشعير والجاودار، مما يؤدي إلى استجابة مناعية تدريجية تلحق الضرر بالأمعاء الدقيقة ويمكن أن تؤثر أيضًا على أعضاء أخرى. تعد العلامات الكيميائية الحيوية الدقيقة ضرورية للتشخيص وتقييم المخاطر وتنفيذ العلاجات الفعالة لتعزيز النتائج السريرية. هدفت هذه الدراسة إلى تقييم التغيرات في مستويات الدم من اليوريا والكرياتينين والشوارد (الصوديوم

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والبوتاسيوم والكلوريد) والعناصر النزرة (المغنيسيوم والزنك) وفيتامين سي لدى الأفراد العراقيين الذين تم تشخيصهم بمرض الاضطرابات الهضمية. تمت مقارنة 100 مريض مصاب بمرض الاضطرابات الهضمية الذين لم يتبعوا نظامًا غذائيًا خاليًا من الغلوتين بـ 57 من ألأشخاص الأصحاء. أظهرت النتائج زيادة كبيرة في مستويات اليوريا والكرياتينين في المصل ($p < 0.05$)، في حين ظلت مستويات الشوارد دون تغيير. وعلى العكس من ذلك، انخفضت مستويات العناصر النزرة (المغنيسيوم والزنك) ومستويات فيتامين سي في المصل بشكل ملحوظ في كل من المرضى الإناث (PI) والمرضى الذكور (PII) مقارنة بمجموعاتهن الصحية من الإناث (CI) والذكور من مجموعة ألأصحاء (CII). تشير هذه النتائج إلى أن الاختلافات الملحوظة قد تكون مرتبطة بزيادة خطر الإصابة بخلل في وظائف الكلى بسبب ارتفاع مستويات اليوريا والكرياتينين في المصل لدى الأفراد المصابين بمرض الاضطرابات الهضمية

Introduction

Chronic inflammatory diseases in the intestine have become increasingly common over the past 30 years, affecting both the small and large intestines. Celiac disease (CD) is the most common chronic inflammatory disorder of the intestinal tract. A key feature of these diseases is their impact on the epithelial barrier [1]. CD results from the consumption of certain food components, particularly grains containing gluten (wheat, barley, and rye), in conjunction with a genetic predisposition that triggers a gradually progressive autoimmune response affecting the intestines and other organs[2].

Individuals with CD typically carry the HLA-DQ2 allele (90-95%), while others may have the HLA-DQ8 variant[3]. The CD is characterized by chronic inflammation primarily affecting the small intestine, which can lead to nutrient malabsorption, chronic or intermittent diarrhea, stopped growth or short stature, iron deficiency, weight loss, and osteopenia[4]. The small intestine is crucial plays a crucial role in the digestion, secretion, and absorption of nutrients. Numerous mucosal folds with villi increase absorption area and increase the production of digestive enzymes [5].

Some patients exhibit typical symptoms related to micronutrient malabsorption and show variations in the natural history of the disease. Although symptoms can manifest at any stage of life, CD typically has two distinct stages of emergence at different ages. The first occurs early in life, around the age of two (after introducing a gluten-containing diet), and the second occurs later, up to the 40th age. Symptoms may first appear after prolonged diarrhea following gastroenteritis or after abdominal surgery[6]. For individuals with CD, adhering to a gluten-free diet is essential [7]. Serological tests, including anti-endometrial antibodies (EMA), and anti-tissue transglutaminase antibodies (TTG), play a critical role in the diagnosis and screening of CD, these tests have been validated and remain useful in clinical practice[8]. The disease prevalence rate of CD is 1.4%, and it is more common in children than adults[9]. Patients with CD have been found to have increased intestinal permeability[10] and abnormal Tight Junction (TJ) structure. This may lead to dysregulation of paracellular signaling pathways, which may be a primary or secondary finding related to gliadin uptake. Additionally, individuals with CD are more susceptible to suffering from mental illness, depression, and infertility[1].

There are established connections between chronic kidney disease (CKD) and CD[11]. Kidney functions include excreting excess fluid and waste through the urine, regulating blood salt levels, controlling blood pressure, and regulating certain hormonal processes such as vitamin D activation [12]. Impaired regulatory function in CKD can lead to changes in electrolyte and acid-base balance and can be life-threatening[13]. Biochemical markers are

essential for accurate diagnosis, risk assessment, and introducing treatments that improve clinical outcomes. For regular analysis, renal function markers such as creatinine, urea, and electrolytes are employed[14]. Patients who have undergone distal gastrectomy may experience constriction of the gastric mucosa, which can hinder their ability to absorb water. This reduced water absorption may result in elevated levels of renal function tests, indicating potential kidney issues[15]. Urea and creatinine are non-toxic substances that are suitable for measuring kidney function. Electrolytes include positive, and negative charged ions produced in cells and extracellular fluids such as plasma, blood, and intestinal fluid. The measurement of electrolytes is used to assess kidney function[16].

Trace elements such as manganese, iron, cobalt, copper, zinc, and molybdenum, as well as the bulk metallic sodium, potassium, calcium, and magnesium, are important to human health[17-18]. Bread and flour are important sources of energy that contain protein, fiber, carbohydrates, and minerals such as magnesium, potassium, zinc, copper, potassium, sodium, and chloride[19]. Vitamin C malabsorption in celiac disease can occur due to damage to the lining of the small intestine, potentially resulting in a deficiency. As a result, individuals with celiac disease may require vitamin C supplements to maintain optimal levels and support their immune function[20]. This study aimed to find an association between celiac disease and the disturbance of kidney functions.

2. Materials and Methods

From November 2023 to February 2024, a patient collection was placed in the Medicine City Hospital (Liver and digestive system department) in Baghdad, Iraq. The study included patients with a confirmed history of CD (P, n=100), PI (Female=51), PII (Male = 49), and healthy individuals (C, n=57), CI (Female=35), CII (male=22) were included in this study. Endoscopic biopsy was performed on all patients to diagnose CD and according to clinical tests or biopsies, every patient was compliant. All patient groups had a disease duration of (1–10) years and were not committed to the gluten-free diet.

2.1. Excluded from this Study:

Individuals with controlled hypertension, diabetes, hepatitis, cancer, and patients suffering from gastrointestinal disease, active inflammatory conditions, irritable bowel syndrome, and kidney disease as well as smokers and alcohol consumption that could have hindered this study were excluded from the study.

2.2. Collection of Blood Samples:

After an 8–10 hour fast, five millilitres of blood were collected from each participant in this study (aged 5-55 years) through venipuncture. A gel tube containing the blood sample was filled and was permitted to solidify at room temperature. To estimate renal functions, electrolytes, trace elements, and vitamin C, every gel tube underwent centrifugation at 3000 r. p. m. for 10 minutes to get serum.

2.3. Laboratory Tests:

Anti-TTG (IgG) levels were assessed using the ASKULISA ELISA kit (Germany). Kidney functions (Urea and Creatinine) were determined using Linear Chemical, Spain kit. Trace elements: magnesium was determined using (Bio Vision), Zinc was determined using (Elab Science) and electrolytes were determined by an automated procedure using a Fuji device (Germany). Serum vitamin C levels were determined using a DTCS detector [a combination of 2,4-dinitrophenylhydrazine (2%) + thiourea (5%) + copper sulfate (0.6%)] at λ = 520 nm, by Nino and Shah's approach[21-22]. The metaphosphoric acid (6%) was substituted with trichloroacetic acid (TCA) (6%), as the standard curve was used to determine

the vitamin C concentrations in the samples, with results expressed in g/L using vitamin C as a standard.

2.4. Analytical Statistics

Version 22 of the (SPSS) software was used to analyze the data quantitatively. The means ± standard deviation (mean ± SD) for the stair-changing was reported. To compare groups, the Tukey test and one-way ANOVA were used. A statistically significant difference was identified when the P-value was below 0.05.

3. Results

In this study, 157 Iraqi participants aged group 5 -55 years were divided into two groups: the healthy group (n=57, C), patients who had historical disease periods between 1-10 years (n=100, P). These groups were subdivided into healthy females (CI), healthy males (CII), patient females (PI), and patient males (PII). The results, presented in Table 1, indicate that there is no statistically significant in the age between all the studying groups (P>0.05).

Table 1: Compared information between healthy controls and celiac patients

Parameters	Healthy Female CI(n=35)	Patients Female PI(n=51)	Healthy Male CII(n=22)	Patients Male PII(n=49)	Groups	P-value
Age (Year)	24.91± 11.53	22.84± 8.65	22.59± 12.09	23.46± 12.99	CI&PI	0.837
					CII&PII	0.990
					PI&PII	0.992
Anti-TTG (IgG)(U/l)	4.01± 3.40	103.97± 92.51	8.18± 11.87	111.93± 117.66	CI&PI	0.000
					CII&PII	0.000
					PI&PII	0.965
Urea (mg/dL)	26.66± 8.78	56.84± 11.79	24.73± 12.73	67.13± 1.63	CI&PI	0.000
					CII&PII	0.000
					PI&PII	0.000
Creatinine (mg/dL)	0.67± 0.37	2.38± 0.30	0.55± 0.16	2.39± 0.36	CI&PI	0.000
					CII&PII	0.000
					PI&PII	0.997
Na (m Eq/L)	137.94± 1.42	138.74± 1.89	138.13± 2.08	139.21± 1.21	CI&PI	0.116
					CII&PII	0.052
					PI&PII	0.488
K (mmol/L)	4.28± 0.51	4.06± 0.61	4.27± 0.58	4.01± 0.68	CI&PI	0.347
					CII&PII	0.357
					PI&PII	0.982
Cl (m Eq/L)	140.40± 25.50	135.07± 30.20	142.07± 5.25	132.99± 27.11	CI&PI	0.787
					CII&PII	0.527
					PI&PII	0.978
Mg (nmol/ml)	1.77± 0.30	0.79± 0.18	1.84± 0.22	0.77± 0.18	CI&PI	0.000
					CII&PII	0.000
					PI&PII	0.971
Zn (µmol/L)	0.81± 0.24	0.33± 0.07	0.86± 0.16	0.30± 0.05	CI&PI	0.000
					CII&PII	0.000
					PI&PII	0.756
Vitamin C (mg/dL)	4.21 ± 0.23	3.78± 0.55	4.16± 0.48	3.52± 0.78	CI&PI	0.007
					CII&PII	0.000
					PI&PII	0.102

CI: Control Female, PI: Patients Female, CII: Control male, PII: Patients male, Significant: *P<0.05 **P<0.001; no significant in P>0.05.

The levels of anti-tissue transglutaminase (IgG) showed a significant increase (P=0.000) in PI(103.97±92.51 U/l) compared to CI(4.01± 3.40U/l) and in PII(111.93±117.66U/l) compared to CII (8.18±11.87U/l). Additionally, there was no significant difference(P=0.965) between PI and PII groups. Kidney functions, as indicated by serum urea levels, revealed a highly significant difference (P=0.000) in PI(56.84± 11.79 mg/dL) compared to CI(26.66± 8.78mg/dL) and in PII(67.13± 1.63 mg/dL) compared to CII (24.73± 12.73mg/dL). In addition, there was a highly significant difference(P=0.000) between PI and PII groups. Serum creatinine levels exhibited a significant increase (P=0.000) in PI(2.38±0.30 mg/dL) compared to CI(0.67±0.37 mg/dL) and in PII(2.39± 0.36 mg/dL) compared to CII(0.55±0.16 mg/dL), but there was no significant difference(P= 0.997) between PI and PII groups. Serum electrolytes such as serum Na levels showed no significant difference(P=0.116) between PI (138.74±1.89 mEq/L) and CI(137.94± 1.42 mEq/L) and between PII (139.21± 1.21 mEq/L) and CII (138.13±2.08 m Eq/L) (P=0.052). Moreover, no significant difference (P=0.488) between the PI and PII groups was observed. Serum K levels showed no significant difference (P=0.347) between PI (4.06±0.61mmol/L) and CI (4.28±0.51 mmol/L), also between PII (4.01±0.68 mmol/L) and CII (4.27±0.58 mmol/L) (P=0.357)). In addition, there is no significant difference (P=0.982) between the PI and PII groups. Serum Cl levels showed no significant difference (P= 0.787) between PI (135.07±30.20mEq/L) and CI (140.40± 25.50 m Eq/L), also between PII (132.99±27.11 m Eq/L) and CII (142.07±5.25 m Eq/L) (P=0.527). In addition, there is no significant difference (P=0.978) between the PI and PII groups. Trace elements such as Mg showed an extremely significant increase (P=0.000) in PI (0.79± 0.18 nmol/ml) compared to CI (1.77±0.30 nmol/ml) and in PII (0.77± 0.18 nmol/ml) compared to CII (1.84±0.22 nmol/ml). In addition, there is no significant difference (P=0.971) between the PI and PII groups. Serum Zinc levels showed an extremely significant increase (P=0.000) in PI (0.33±0.07 µmol/L) compared to CI (0.81±0.24 µmol/L) and showed a significant increase (P=0.000) in PII (0.30±0.05 µmol/L) as compared with CII (0.86±0.16 µmol/L). In addition, there is no significant difference (P=0.756) between the PI and PII groups. Finally, serum vitamin C levels showed a highly significant decrease (P=0.007) between PI (3.78± .55 mg/dL) compared to CI (4.21 ±0.23 mg/dL) and between PII (3.52±0.78 mg/dL) compared to CII (4.16±0.48 mg/dL) (P=0.001). Additionally, there was no significant difference (P=0.102) between the PI and PII groups.

The correlations were studied, and the findings showed that in the PI group, only creatinine had a positive correlation with anti-tissue transglutaminase (IgG) ($r = 0.380$, $P = 0.006$), while Na ($r = -0.312$, $P = 0.026$) and Zn ($r = -0.315$, $P = 0.024$) had negative correlations with anti-TTG (IgG). Additionally, no significant correlations were found among the other parameters, as shown in Table 2.

Table 2: Correlation between various parameters with Anti-TTG (IgG) in the PI group.

Parameters	Anti-TTG (IgG)	
	r	p
Age (Year)	0.138	0.334
Urea (mg/dL)	-0.121	0.398
Creatinine (mg/dL)	0.380**	0.006
Na (m Eq/L)	-0.312*	0.026
K (mmol/L)	-0.080	0.575
Cl (m Eq/L)	-0.038	0.789
Mg (nmol/ml)	-0.077	0.590
Zn (µmol/L)	-0.315*	0.024
Vitamin C (mg/dL)	0.003	0.986

PI: Patients Female, Significant: *P≤0.05, **P≤0.001; no significant P>0.05

In addition, in the PII group, anti-tissue transglutaminase (IgG) correlated positively with age (r = 0.515, P = 0.000) and negatively correlated with Cl (r = -0.369, P = 0.009). Furthermore, no significant correlations were found between the other parameters, as shown in Table 3.

Table 3: Correlation between various parameters with Anti-TTG (IgG) in the PII group.

Parameters	Anti-TTG (IgG)	
	r	p
Age (Year)	0.515**	0.000
Urea (mg/dL)	0.269	0.062
Creatinine (mg/dL)	0.180	0.215
Na (m Eq/L)	-0.083	0.570
K (mmol/L)	-0.273	0.057
Cl (m Eq/L)	-0.369**	0.009
Mg (nmol/ml)	0.229	0.114
Zn (µmol/L)	0.270	0.061
Vitamin C (mg/dL)	0.130	0.375

PII: Patients Male, Significant: *P≤0.05, **P≤0.001; no significant P>0.05

Discussion:

The CD is a chronic small intestinal disease resulting from an immune-mediated pathology. The disease is caused by persistent gluten sensitivity in genetically susceptible people and is triggered by ingesting gluten, a complex protein found in grains such as barley wheat, and rye [23]. Anti-tissue transglutaminase is a protein immunoprecipitated from fibrosarcoma cells metabolically labelled with IgA from CD patients and is associated with significant, if not the only, endomysial autoantibodies. This led to the identification of tissue transglutaminase as an antigen. In this study, anti-TTG levels were elevated in all patient groups compared to the healthy groups. Additionally, no significant difference in anti-TTG levels was observed between the PI and PII groups. Previous research suggests that measuring IgG anti-TTG antibodies using human TTG effectively detects celiac disease (CD) in individuals with IgA deficiency, which is consistent with our findings [24]. Other previous studies suggest that patients with selective IgA deficiency should be tested by anti-TTG IgG, deaminated gliadin peptides (DGP) IgG, or anti-endomysial antibodies (EmA) IgG, as these have similar

diagnostic accuracy for identifying CD. A positive screening for IgG antibodies, followed by a duodenal biopsy, can confirm the diagnosis of the occurrence of villous atrophy[24]. Additionally, while IgG-EMA and IgG-anti-TTG are useful for initial screening, they are less effective in monitoring dietary compliance with a gluten-free diet[25]. In contrast, another study demonstrates the reduction in levels of TTG autoantibody resulting from a gluten-free diet[26]. The IgG anti-TTG measurements should be incorporated into diagnostic and screening protocols to ensure the identification of these patients, and CD should be considered in all individuals with IgA deficiency[27]. The concentration of tissue transglutaminase antibodies increases with the degree of disease progression and intestinal damage due to sensitivity to gluten proteins but is independent of patient gender[28]. In the present study, kidney function results indicated a significant increase in serum urea levels in all studied patient groups compared to the control groups. The results also revealed that serum creatinine levels showed a very significant increase in all patient groups compared to the control groups; however, there were no notable differences between the PI and PII groups and this is consistent with a private study, patients who consumed gluten observed a slight rise in uric acid, creatinine, and urea. This could suggest impaired renal function, which would be an early sign that CD starting to affect kidney function[29-30]. Another study observed that in people with gluten, Creatinine levels appeared to increase, reflecting the onset of CD and its effect on kidney function[29]. Strong acids (HCl; pH around 0.8) are produced in the stomach by electrolytes (sodium, potassium, and chloride). The primary mechanism behind the production of hydrochloric acid in parietal cells is the hydrogen-potassium pump. As a result, proton pump inhibitors that block the pH proton pump reduce stomach pH and encourage H. pylori growth and gastric mucosal invasion[31]. Serum electrolytes such as serum Na, K, and Cl levels showed no significant difference between all the studied groups. The present study revealed that sodium and chloride were negatively correlated with anti-TTGs, This aligns with a previous study that reported electrolyte alterations such as hypokalemia, hypomagnesemia, hypocalcemia, and hyper/hyponatremia[32]. The disease manifests as severe dehydration, neurological dysfunction, renal failure with a creatinine level greater than 2.0 g/dL, significant weight loss as well as recurrent diarrhea[32]. Although there was no celiac crisis, the patient in this case had hyponatremia and borderline normal potassium levels. The amount of sodium consumed and bone mineral density were discovered to be significantly correlated with osteopenia and celiac disease[33]. Previous studies have shown that electrolyte disturbances are often linked to malnutrition, with the most common imbalances affecting serum levels of potassium, bicarbonate, and sodium [34]. previous studies have shown that an imbalance in the level of electrolytes in the blood causes various diseases. Since most kidney infections/diseases are “silent,” it is not uncommon for subclinical cases of kidney inflammation to be exacerbated by autoimmune diseases that cannot be avoided as part of the recovery process with the Marshall protocol[35] and a prior study revealed that CD can appear suddenly with severe malabsorption syndrome, electrolyte problems, and hypoproteinemia. This suggests that even a chronic illness, such as CD, may have an acute beginning in a few patients. Although uncommon in clinical practice, this sudden start of CD needs hospitalization and prompt treatment (such as electrolyte replacement and protein correction) to prevent life-threatening consequences[36]. A prior study also found that CD might cause electrolyte abnormalities, which can result in arrhythmias, impaired mental status, and mortality. This can be seen in the celiac crisis, a rare, but significant complication of CD produced by acute metabolic disruption[32]. Trace elements such as Mg showed high significance levels in all the studied groups. Furthermore, there was no significant difference between the PI and PII groups, which is inconsistent with previous studies that have shown Mg deficiency in approximately 20% of untreated celiac disease patients[37], and a study by Rujner *et al.* showed that the incidence of magnesium deficiency in treated adult CD patients was similar to that of

untreated patients and controls (4). In addition, previous investigations showed, that trace elements (Zn, Mg) have vital functions in strengthening the immune system, and hence their inadequacies may enhance a host's risk of infectious illnesses[38]. Patients with digestive disorders suffer from deficiencies in vitamins and minerals, including zinc[39]. In our study, serum zinc levels significantly decreased in all studied groups. Studies have indicated that individuals with CD who are receiving treatment as well as those who are not have lower levels of plasma zinc[40], this is at odds with what we found. Zinc deficiency (ZD) has been shown to afflict up to 64% of pediatric patients with CD and to spread as much as 67% in newly diagnosed adult patients[40]. According to Stenberg *et al.,* ZD may stimulate the transglutaminase-2 (TG2) enzyme, which zinc normally inhibits, particularly in the intestinal mucosa. When this activation occurs, a TG2-thioester intermediate-deamidated gliadin complex is formed. This complex functions as a "neo-antigen," inciting an immune response in those who are genetically vulnerable and causing inflammation and villous atrophy[40]. The current study showed that serum vitamin C levels have significantly decreased in the studied groups. Gastric pH is the most important factor affecting the decrease in vitamin C levels in contagious fluid observed in hypochlorhydria. Increased pH in the stomach converts vitamin C to a less active form, irreversibly inactivating ingested vitamin C[41]. The study by Waring *et al.,* also suggested enucleation of Helicobacter pylori(H. pylori)can increase vitamin C levels in contagious fluid[31]. H. pylori infection has been shown to reduce vitamin C levels in gastric fluid, as shown in a previous study[42]. In a study, Bernardo *et al.,* Company tested the evaluation to which vitamin C helped reduce mucosal inflammation in individuals suffering from celiac disease[43]. In the initial phases of an immunology action, vitamin C stimulates phagocytosis, shields neutrophils from oxidative stress, and forms reactive oxygen species (ROS) that destroy antigens[44-45]. The most common nutritional deficiency in CD are vitamin D, E, and micronutrients. Pseudo-cereals like quinoa and amaranth are cheap alternatives to GFD and are considered good sources of specific micronutrients, such as folate, riboflavin, vitamin C, and vitamin E[46-47].

Conclusion

The current findings indicate that individuals with CD may be at an increased risk of renal dysfunction, as indicated by elevated serum urea and creatinine levels. This highlights the necessity for further research into the relationship between CD and kidney health. Additionally, while no significant differences were observed in electrolyte levels, the negative correlation between sodium and chloride with anti-TTG antibodies suggests that gastric pH may influence vitamin C levels in CD patients. Therefore, further investigation is warranted to understand the complex relationships between a gluten-free diet and vitamin C status in these individuals.

Ethics

The Iraqi ministries of health, the environment, higher education, and scientific research have ethically approved the Research Moral Committee for scientific study.

Conflict of Interest

The writers affirm that there is no conflict of interest involving them.

The study protocol was approved by the Regional Ethics Committee of Tampere University Hospital (R16090). As the study was register-based, no consent from patients was required.

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