# Copeptin (Not Only) in Water and Sodium Disorders

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ABSTRACT
Arginine vasopressin (AVP) is a key regulator of fluid balance and vascular tone. Its diagnostic utility in various disorders is limited by its short half-life, pulsatile secretion, and preanalytical instability. Copeptin, the C-terminal fragment of preprovasopressin, is secreted in equimolar amounts with AVP and offers a stable, easily measurable surrogate marker. This review highlights the clinical relevance of copeptin in the differential diagnosis of polyuria-polydipsia syndrome, hyponatraemia, critical illness, cardiovascular disease and diabetes mellitus. Copeptin improves diagnostic accuracy, particularly in differentiating types of diabetes insipidus and in the early exclusion of acute myocardial infarction. It also shows prognostic value in heart failure, stroke, and diabetic complications. Given its broad diagnostic potential and analytical advantages, copeptin represents a valuable biomarker for AVP-related pathologies.

KEYWORDS
Copeptin; polyuria; polydipsia; diabetes insipidus; hyponatraemia; SIADH

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## VASOPRESSIN

Arginine vasopressin (AVP), or antidiuretic hormone (ADH), regulates fluid homeostasis and vascular tone. It is a peptide hormone produced mainly by magnocellular neurosecretory neurons of the hypothalamic supraoptic nucleus and subsequently stored in the posterior pituitary, from where it is then secreted into the circulation. It regulates osmolarity via the arginine vasopressin 2 receptor (V2) in the kidneys, promoting water reabsorption from tubular fluid (1). Part of the AVP is also directly secreted from parvocellular neurons of the paraventricular nucleus into the hypothalamic-hypophyseal portal system, stimulating the production of adrenocorticotropic hormone (ACTH) and prolactin via the arginine vasopressin 1b receptor (V1b) (2). AVP also affects vascular tone, platelet aggregation, and factor VIII release via the endothelial arginine vasopressin 1a receptor (V1a) (3) (Figure 1). Additionally, AVP participates in the regulation of inflammation and exhibits several neuro-behavioural properties that remain to be studied.

As a result of the aforementioned, AVP plays a major role in the pathophysiology of several water and sodium disorders. Therefore, measuring AVP levels in such disorders could significantly help in differential diagnosis. However, direct measurement of AVP levels is significantly limited by its short half-life of approximately 24 minutes (4), secretory pulsatility, and rapid in vitro degradation, which requires complicated preanalytical steps and makes interpretation rather difficult. Hence, there has been a search for a surrogate marker, and copeptin seems to be the most promising one.

## COPEPTIN

Copeptin (or CT-proAVP) is a 39 amino acid long glycosylated fragment of preprovasopressin (5). This prohormone is synthesised in the hypothalamic nuclei, packed into neurosecretory granules, and then proteolytically cleaved to copeptin alongside AVP and neurophysin II during transport to the posterior pituitary (Figure 2). Copeptin was first described in 1972 (6), but despite 50 years of intense research, its physiological role remains unknown, although it may possibly contribute to the three-dimensional folding of AVP (7). Copeptin secretion is equimolar to AVP in response to the same stimuli (high plasma osmolarity, low blood volume, stress, angiotensin II, etc.). Furthermore, it has a longer half-life with stable plasma concentrations and slower in vitro degradation (8), making it an ideal marker for AVP release.

There are several methods for measuring copeptin, but unfortunately, not all of them yield the same results. Currently, most studies use automated immunofluorescent assay (KRYPTOR), a successor to the original sandwich immunoluminometric assay (LIA) (9). There are also various enzyme-linked immunosorbent assays (ELISAs) that, however, have shown poor diagnostic accuracy, which is why they are generally not recommended. The commonly used cut-off values for copeptin were established using LIA or KRYPTOR (from 1.0 to 13.8 pmol/l with higher median levels in men than in women) (9).

## POLYURIA-POLYDIPSIA SYNDROME

The polyuria-polydipsia syndrome is a condition characterized by excessive urination (polyuria) greater than 3 litres per day, in combination with excessive water intake due to increased thirst (polydipsia). Though polyuria can be caused by several different conditions, the polyuria-polydipsia syndrome in the narrower sense includes only primary polydipsia and central and nephrogenic diabetes insipidus (10). Primary polydipsia is caused by habitual or compulsive excessive fluid intake because of

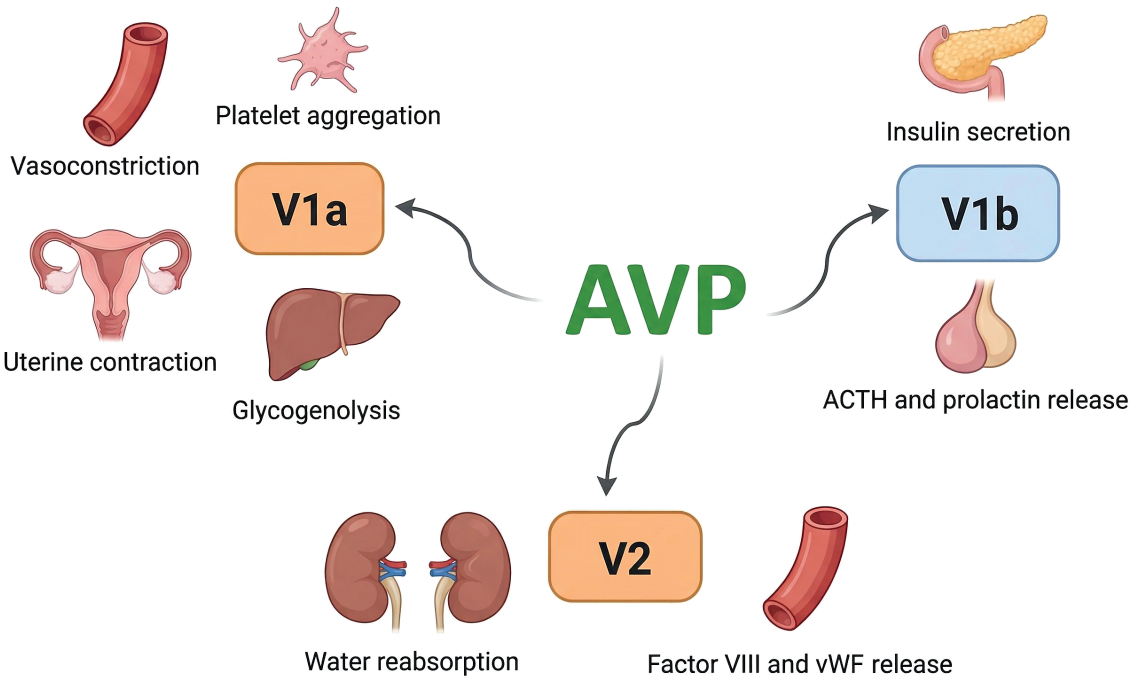


**Fig. 1** Overview of AVP receptors.

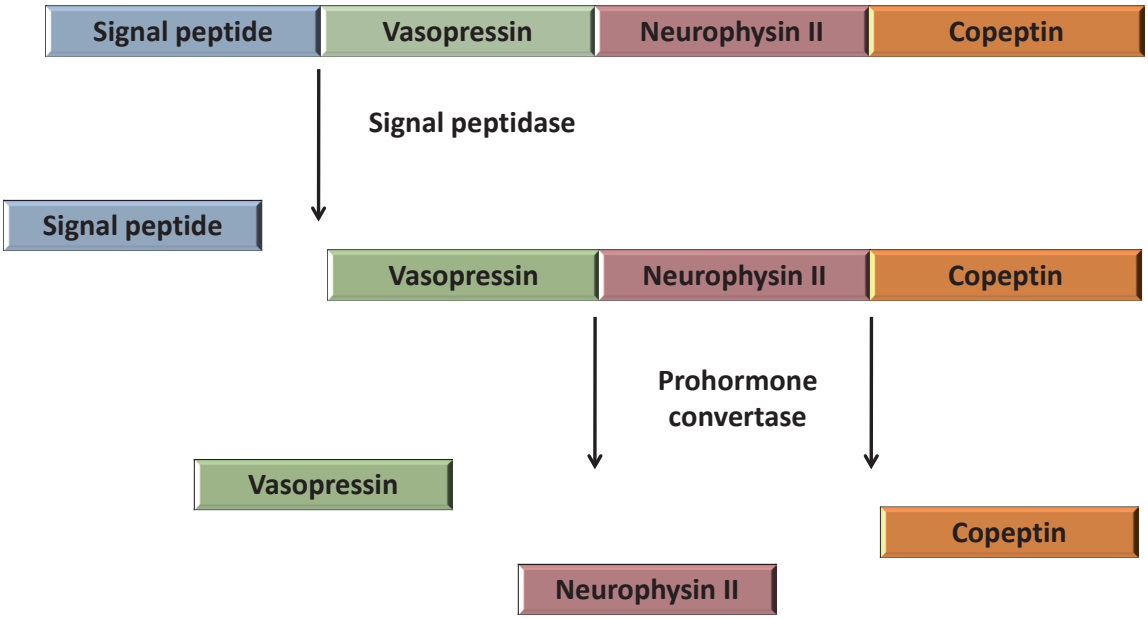


**Fig. 2** Synthesis of copeptin from preprovasopressin.

a psychological disorder (psychogenic polydipsia) or due to a hypothalamic disorder affecting the centre of thirst (dipsogenic polydipsia). Central diabetes insipidus (AVP deficiency) is caused by insufficient AVP secretion in the hypothalamus or by damaged pituitary stalk, typically due to tumorous, inflammatory, or haemorrhagic conditions. Nephrogenic diabetes insipidus (resistance to AVP) is characterized by the kidneys' insensitivity to AVP, caused by metabolic issues, certain drugs, or multiple kidney disorders (11).

Correctly distinguishing between these entities is crucial because inadequate treatment could lead to further complications. However, the differential diagnosis can be quite difficult. Medical history and physical examination are helpful but usually not enough; that is why functional tests were developed. The most widely used is the water deprivation test, followed by the desmopressin test. The water deprivation test helps to distinguish between primary polydipsia and diabetes insipidus, and the desmopressin test can discriminate between central and nephrogenic

| **Preparation** |
|---|
| Withhold drugs effecting urine output for at least 24 hours (diuretics, glucocorticoids, SGLT-2 inhibitors). |
| Patient lies in supine position. Two intravenous cannulas: one for blood sampling and the other for infusion. |
| Baseline serum sodium, glucose, urea, plasma osmolality and copeptin are obtained prior to infusion. |
| **Hypertonic saline infusion phase** |
| Bolus dose of 250 ml 3% saline is given over 15 minutes, followed by 0.15 ml/Kg/min. |
| Serum sodium and osmolality are measured every 30 minutes. |
| The infusion is stopped if the serum sodium increases to >150 mmol/L. |
| Stimulated plasma copeptin is measured after the infusion is stopped. |
| Heart rate and blood pressure are continuously monitored throughout the phase. |
| **Hypotonic fluid administration phase** |
| Patient is asked to drink water at 30 ml/Kg within 30 minutes. |
| This is followed by intravenous infusion of 5% glucose at 500 ml/hour for 1 hour. |
| Serum sodium is measured after the completion of 5% glucose infusion to ensure its return to normal values. |
| Heart rate and blood pressure are continuously monitored throughout the phase. |

**Fig. 3** Example of hypertonic saline test protocol (14).

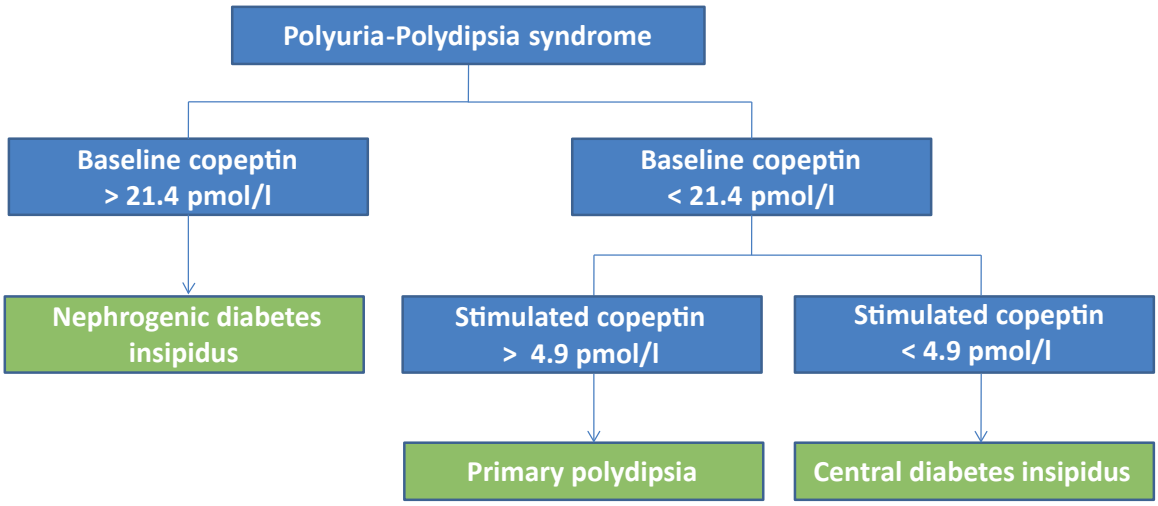


**Fig. 4** Diagnostic algorithm of polyuria-polydipsia using copeptin.

diabetes insipidus. The water deprivation test has a decent sensitivity for severe central diabetes insipidus, but its sensitivity decreases in partial forms (12). On top of that, it could be stressful, uncomfortable, and potentially dangerous for the patient as it requires strict fluid restriction for up to 18 hours according to some protocols. Therefore, a search has been conducted for a surrogate test to replace water deprivation, and that is where copeptin comes into play.

Without prior testing, a baseline copeptin level greater than 21.4 pmol/L differentiates nephrogenic diabetes insipidus from other aetiologies with 100% specificity and sensitivity (13), making the desmopressin test unnecessary. Discrimination of central diabetes insipidus from primary polydipsia still requires functional testing, but the water deprivation test can be avoided using the 3% saline test. There are several protocols for the 3% saline infusion test that differ in infusion rates, frequency of monitoring, and the cut-off for infusion termination. However, the principle is still the same. After baseline blood sampling, you must create a state of hyperosmolarity and mild hypernatremia by administering a 3% saline infusion to stimulate AVP secretion (evaluated by copeptin). Frequent blood sampling is necessary to stop infusion in a timely manner to maintain safety (Figure 3). After taking the final sample, water intake is resumed, and 5% glucose is usually administered to restore normal fluid balance. Stimulated copeptin levels greater than 4.9 pmol/l can differentiate patients with central (complete or partial) diabetes insipidus from patients with primary polydipsia with 94% specificity and 94.4% sensitivity (13), exceeding the accuracy of the water deprivation test (Figure 4).

## HYPONATRAEMIA

The differential diagnosis of hyponatraemia (serum sodium less than 135 mmol/l) is quite broad; however, most of the conditions causing hyponatraemia are associated with an excess of AVP. That includes mainly the syndrome of inappropriate AVP secretion (SIADH) and conditions with decreased effective circulating volume, such as severe dehydration, congestive heart failure, or liver cirrhosis (these can stimulate AVP secretion even without hyperosmolarity) (15). Thus, measuring copeptin in hyponatraemic patients seemed obvious and promising.

Copeptin shows the strongest diagnostic value in patients with hyponatraemia due to primary polydipsia, because of suppressed AVP secretion (16). Among patients with AVP-dependent hyponatraemia, those with sodium depletion show significantly higher median copeptin values than those with SIADH. However, there is a significant overlap between these two groups, making it challenging to establish reliable cut-off values. The copeptin-to-urinary sodium (copeptin / U-Na) ratio appears more promising. According to Fenske et al., a ratio of copeptin to urinary sodium (copeptin/U-Na) ratio of less than 30 pmol/mmol is superior to previously used markers (urinary sodium, serum urate level and fractional uric acid and sodium excretion) in distinguishing primary from secondary copeptin release (16, 17). Another diagnostic challenge is to distinguish SIADH from diuretic-induced hyponatraemia. In this case fractional uric acid excretion is still the most reliable option, because copeptin levels do not differ significantly between the two groups (16).

## CRITICAL ILLNESS AND CARDIOVASCULAR DISEASE

Considering stress as one of the stimuli for AVP secretion, copeptin levels may serve as a decent biochemical marker of stress. There is an increasing amount of data to support the concept. According to Ristagno et al. (18), copeptin levels on admission to the ICU were significantly higher than those in the control group. Higher admission copeptin was associated with ICU death and predicted subsequent organ dysfunction (similar to free cortisol levels).

The role of copeptin in the diagnosis of acute myocardial infarction is increasing as well. Copeptin performs even better than troponin I (TnI) in ruling out myocardial infarction in patients within the first two hours after

the onset of chest pain. Additionally, the combination of copeptin and TnI improved diagnostic performance even more (19, 20).

In heart failure, higher copeptin correlates with a worse prognosis and risk of hospitalisation, so in the future it could possibly be used as a predictor of adverse outcomes and help to assess the severity of heart failure (21). According to Schill et al., copeptin can even predict the development of heart failure in older adults (22).

Copeptin is also helpful in distinguishing stroke patients from stroke-free patients in the emergency department environment. However, the levels of copeptin do not correlate with the severity of the stroke and outcome of the patient (23).

## DIABETES MELLITUS

Vasopressin actively participates in glucose metabolism by promoting glycogenolysis and gluconeogenesis in the liver (via the V1a receptor) and increasing both glucagon and insulin (depending on glycemia) secretion in the pancreas (via the V1b receptor) (24). That is probably why elevated copeptin is an independent predictor of type 2 diabetes mellitus development. It may also be helpful in assessing complications of diabetes mellitus, as higher copeptin levels positively correlate with glycosylated haemoglobin, serum creatinine and the urinary albumin to creatinine ratio, and negatively with glomerular filtration rate (25). Thus, it could be used as a predictor of renal function deterioration in diabetic patients.

## CONCLUSION

Copeptin has emerged as a reliable and clinically valuable surrogate marker for arginine vasopressin, overcoming the limitations of direct AVP measurement. Its diagnostic and prognostic utility spans a wide range of conditions, including water balance disorders, hyponatraemia, cardiovascular disease, and diabetes mellitus. With its stability, ease of measurement, and strong correlation with AVP secretion, copeptin offers a powerful tool for improving diagnostic accuracy and guiding patient management in both acute and chronic settings. Considering the current knowledge and ongoing research, the use of copeptin in clinical practice is expected to continue expanding.

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# Biomechanics of Arteriovenous Fistula: An Overview of Hemodynamic and Remodeling Mechanisms

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ABSTRACT

Arteriovenous fistulas (AVFs) are widely accepted as the gold standard for vascular access in chronic hemodialysis patients due to their superior long-term patency and low complication rates. However, up to half of all created AVFs fail to mature adequately, and many develop late complications such as stenosis, thrombosis, or aneurysmal degeneration. This review provides an overview of the AVF development process, focusing on the biomechanical forces that drive vascular remodeling and contribute to maturation and pathological changes. We summarize the role of endothelial mechanotransduction and insights from recent studies that reveal how wall shear stress (WSS) patterns and oscillatory flow relate to the genesis of neointimal hyperplasia and later stenosis. Understanding these mechanobiological processes has led to novel surgical techniques, anastomosis design optimization, and better cannulation strategies. Although the knowledge of hemodynamic-biological interactions remain limited, further research can offer directions for better AVF performance.

KEYWORDS

arteriovenous fistula; hemodynamics; vascular access; remodeling; wall shear stress

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## INTRODUCTION

The prevalence of patients with end-stage renal disease (ESRD) requiring regular dialysis has been growing, with approximately 550,000 people in Europe being dependent on this treatment (1). The rising count is associated mainly with demographic changes – population aging, and the increasing incidence of diabetes mellitus and hypertension, which are both major contributors to the development and progression of chronic kidney disease (CKD). In patients who advance to ESRD, renal replacement therapy becomes essential to sustain life (2, 3). Today's medical science offers three main treatment options for renal replacement: hemodialysis, peritoneal dialysis, and kidney transplantation (3, 4). While in the past ESRD used to be considered fatal, developments in therapeutic strategies, such as strict treatment-monitoring protocols and advanced modern hemodialysis machines, have made the whole treatment process safe and serious complications rare. Hemodialysis is generally the most commonly used modality, typically performed in specialized outpatient departments of hospitals or clinics, three times per week in sessions lasting approximately four hours. However, the exact regimen serves individual patient needs. Peritoneal dialysis, in contrast, is conducted daily, usually at the patient's home. For example, automated peritoneal dialysis (APD) commonly takes place overnight.

### HEMODIALYSIS (HD)

Hemodialysis, a life-sustaining extracorporeal treatment for patients with ESRD, has become a routine procedure. With modern dialysis equipment, which is accessible worldwide, and established treatment protocols, the incidence of severe complications has markedly decreased (5). In this complex procedure, uremic toxins and excess fluid from the bloodstream are filtered through a semipermeable membrane using counter-current flow of dialysate (5, 6). Small waste products are removed primarily through diffusion, osmosis, and ultrafiltration. During diffusion, waste products move from areas of higher concentration in the blood to areas of lower concentration in the dialysate. Osmosis helps balance fluid levels by allowing water to move across the membrane. Ultrafiltration, generally driven by transmembrane pressure differences, can efficiently extract excess fluid from the vascular system. These combined mechanisms ensure toxin removal and fluid balance maintenance (6).

### DIALYSIS ACCESS

Dialysis access is essential to dialysis, providing a reliable and durable site through which blood can be removed and returned during each procedure. The ideal vascular access should be technically easy to construct, ready for immediate use after construction, and low-maintenance. Unfortunately, none of the available options meet all the criteria mentioned above. There are three main types of dialysis access: arteriovenous fistulas (AVF), arteriovenous grafts (AVG), and central venous catheters (CVCs) (7, 8). To compare these types of vascular access, CVCs can be used immediately, AVGs either also immediately or within two weeks, depending on the chosen prosthesis material, and AVFs require the longest period for maturation, which is four to six weeks (8).

Both AVFs and AVGs are technically demanding to create, while inserting a CVC is considered relatively easy and less invasive. These procedures also differ in terms of patient administration, medical procedure planning, and length of hospital stay. The initial success rate of AVFs is low, but after maturation, they offer high long-term patency. In contrast, AVGs and CVCs have high initial success rates but lower long-term patency, with central vein catheters having the worst performance (8, 9). Blood flow rates are high in AVGs and matured AVFs, but low in CVCs. The probability of infection is lowest with AVFs, higher with AVGs, and highest with CVCs. CVCs also have a high probability of central vein thrombosis (10). AVFs are noted for their high primary patency rates, remaining functional for extended periods without requiring intervention. Long-term, AVFs generally provide better outcomes than AVGs and CVCs. In terms of maintenance, arteriovenous fistulas require fewer interventions to maintain their functionality, whereas arteriovenous grafts and CVCs usually need more frequent upkeep. The selection of the appropriate access type depends on patient-specific factors, including vascular anatomy, existing health conditions, and the expected duration of dialysis. Hemodynamic benefits are significant with AVF as they support higher blood flow rates and have less negative inflow arterial pressure, which contributes to more effective dialysis treatment (11).

## DEVELOPMENT AND MATURATION OF AVF

An AVF is constructed by creating a direct anastomosis between an artery and an adjacent vein, typically in the forearm or upper arm. The arterial blood flow is redirected into the venous system, resulting in elevated flow and pressure that induce progressive vein remodeling. The vein subsequently undergoes hypertrophy and dilation to accommodate repeated cannulation and hemodialysis's high blood flow demands (12).

After surgery arteriovenous fistulas require a maturation period of four to six weeks. However, once matured, they demonstrate superior long-term outcomes, including prolonged patency and lower infection rates with rare need for interventions (8). The mature AVF ought to keep flow rates of approximately 350–450 mL/min to support adequate dialysis. In clinical practice, forearm AVFs commonly achieve flows between 500 and 2000 mL/min, while upper arm AVFs may reach 3000 mL/min (12, 13). Despite proper surgical technique, failure of maturation occurs in approximately 20–50% of AVFs (12, 14). One potentially serious complication is distal ischemic steal syndrome, in which retrograde flow into the venous system deprives the distal extremity of arterial perfusion. In severe cases, this may necessitate surgical revision or ligation of the fistula (15).

Long-term complications, even in well-functioning AVFs, are frequent. Most common complication include stenosis, thrombosis, and aneurysmal degeneration (14, 16).

These complications often arise at sites of repeated puncture or in regions subject to disturbed flow. Aneurysm formation is typically localized to the venous segment of the arteriovenous fistula and may be preceded by intimal hyperplasia and vessel wall thickening (16, 17). Segmental venous dilation may disrupt laminar flow, promoting thrombogenesis. Narrowing of the outflow tract with stenosis results in increased wall tension and may contribute to aneurysmal progression. AVF aneurysms frequently exhibit tortuous morphology, with thinned, friable walls that are prone to rupture if left untreated (16, 17).

## HEMODYNAMIC FORCES AND VASCULAR REMODELING IN AVF MATURATION AND COMPLICATIONS

Processes determining the success or failure of fistula maturation and the patency of the connected vessels are not yet fully understood. However, it is certain that numerous biomechanical factors significantly influence the long-term performance of the vessel junction. Reasons for the principal changes happening to the vein, that is the increase in its diameter and wall thickness, have a clear mechanobiological explanation. The vein, suddenly exposed to arterial, e.g. significantly higher, blood pressure, starts the process of remodeling so that it can withstand the new loading conditions. While the need for change in geometry of the vessel is easy to comprehend, the processes leading to it are not so much. Nevertheless, it has been shown that endothelial cells (ECs) in the intimal layer of the vein play a pivotal role in the intricate mechanism. Forming a contact layer between the blood and the vessel, these cells transcript the mechanical stimuli from the bloodstream into biochemical signals decisive for the vessel's response.

In this paper, the mechanism of remodeling is only discussed from the mechanical point of view, reviewing the literature on the relationship between the properties of blood flow and the vessel's response. For a thorough analysis of the biochemical side of the problematic, readers are referred to other literature, such as Sakurai and Sawamura (18), Pries, Reglin, and Secomb (19), González and Maldonado-Agurto (20), and sources cited therein. From biomechanical perspective, there are two forces acting on the ECs. The force exerted by the blood pressure, causing the vessel wall to dilate and stretch in circumferential direction, and the force arising from the viscous properties of the blood, causing the ECs to be stretched in the direction of the flow. The mechanosensitive nature of the ECs then allows to transduce information of the cell's deformations into chemical signals. The mechanical stimuli in the form of EC stretch change from their physiological state as the vein of AVF is exposed to arterial blood flow, initiating the vessel's remodeling (21, 22).

Since there is a direct relation between the blood-vessel wall interactions and the vessel's pathophysiological response, computational biomechanics have been employed in studies concerning the performance of the AVF. While it is deformations of the ECs that drive the remodeling process, stresses on tunica intima are usually assessed in such studies. The reason why stress is commonly in the focus of the research is that it can be computed without extensive knowledge of the vessel's mechanical properties, at least to a reasonable degree of accuracy (23, 24). Although the radial component of the blood pressure acting on the vessel wall might influence its response, it is the wall shear stress (WSS) that plays the major role in remodeling process (22, 25).

The WSS is caused by the viscous forces exerted by the streaming blood and is defined by its magnitude and direction. Laminar flow can be observed in majority of the circulatory system (26). For both steady and pulsatile laminar flow, the direction of the WSS remains aligned with the axis of the vessel in its straight segments (27). The WSS induced by undisturbed laminar flow is believed to maintain functional homeostasis in the vessel and inhibit EC and vascular smooth muscle cell (VSMC) proliferation (28). Geometric irregularities such as branching disturb the flow, changing its profile. Laminar vortex structures are usually observed in places of irregular geometry. As a result, drops in WSS may be observed at certain spots of vascular branching. Atherosclerotic lesions often develop in areas of low WSS, as has been observed in aortic bifurcations (29,30). Irregularities in the flow (and thus WSS) are introduced as AVF is created, which directly affect the process of vein remodeling and the development of various pathologies.

In principle, the venous part of the AVF is affected by two major changes upon the fistula creation – increase of blood pressure and geometric irregularity. Blood pressure and the average WSS in the vein increase as the vascular junction is created. Elevated WSS can be observed in the vein several centimeters distal to the junction, as demonstrated by numerical simulations (31, 32). In the past, high WSS was associated with the development of intimal hyperplasia, a common cause of AVF failure. However, it has been demonstrated that WSS remains elevated in matured fistulae, regardless of the AVF's outcome (33–35). In contrary, it is believed that steadily high WSS propagates outward remodeling, e.g. increase in diameter and media thickening, as opposed to the unfavorable inward remodeling in the form of VSMCs migration and intimal hyperplasia development (36, 37).

Increase of WSS can be observed in the distal segments of the connected vein. However, more complex stress profile is to be expected at the place of anastomosis and the adjacent swing segment of the vein. Nonuniform disturbed flow develops in area near the junction, with places of high, low, and oscillating WSS present in the region. A high-speed jet strikes the toe region of the vein opposite the anastomosis, inducing WSS of magnitude several times higher than on the surrounding tissue (31, 38). The increased WSS gradient has been shown to correlate with locations of calcified plaque in both artery and vein of the AVF (39).

Although significant increase of WSS is observed at the impact zone of the pulsating blood opposite the anastomosis, a low-velocity region is found in near proximity of the arteriovenous junction (40, 41). A correlation between low average WSS and intimal hyperplasia development was observed in these regions, leading to the belief that it is the decrease of WSS that promotes intimal thickening (42).

However, more recent studies have pointed out that it is not the average magnitude of WSS but rather its change in time that seem to be essential for the ECs biochemical reaction. It has been suggested in computational studies that the place of stenosis is often found in place of oscillatory WSS (32, 40, 43). The oscillations in the WSS direction are caused by the pulsatile nature of the flow, as the vein is introduced to the arterial blood flow pattern. The place of oscillatory WSS coincides with low average WSS as at the pulses only cause changes in magnitude rather than direction in the high-velocity regions. However, although both low and oscillatory WSS can be associated with intimal hyperplasia, it has been demonstrated in an in-vitro study that oscillatory flow leads to a disorganized intima structure development, promoting the inward remodeling that causes stenosis (44). In a unique longitudinal study, Soliveri et al. (45) show that stenosis develops at a place of disturbed flow in a patient over time. They suggest that the observed intimal thickening was caused by WSS instability resulting from disturbances in flow, reinforcing the idea that time-varying WSS is a key predictive marker of the pathological condition.

In summary, using biomechanical tools such as computational simulations, the insight into the pathophysiological processes in AVF has increased significantly in the past two decades. The main research focus has shifted from assessment of the WSS magnitude to the study of its disturbance and oscillations as its instability is linked to the development of vascular stenosis in AVF. The advances in computational methods have also allowed for the newly obtained knowledge on the matter to be used to enhance the techniques and methods used during the surgery and the hemodialysis process. Numerous studies have for example assessed the anastomosis angle and its effect on the blood flow parameters, suggesting that an acute angle of approximately 45 to 75° potentially leads to a more favorable flow pattern in the vein swing segment (46–48). Furthermore, the effect of the blood stream injected during the hemodialysis process at the place of the vascular access has been thoroughly studied, suggesting that further complications can be promoted by the hemodynamic conditions generated around the needle tip (49–51). Thus, although the precise connection between the mechanical stimuli, and the remodeling and pathological processes of the AVF are not yet fully understood, the results of the lates biomechanical studies have already proven to be invaluable for both understanding the mechanobiological principles and enhancing the performance of the arteriovenous junction.

## CONCLUSION

Maintaining the arteriovenous fistula at the desired flow levels for dialysis with minimum complications after years of regular cannulations is still a clinical challenge despite decades of experience, research and upkeep optimizing. It is known that the surgical technique itself and individual patient-related factors, such as vessel quality or local anatomy, play crucial roles in determining AVF outcomes. According to our findings, recent studies of AVF biomechanics have revealed that the wall shear stress, with pressure gradients and flow turbulence, influences endothelial behavior and causes vessel wall remodeling, mainly with disturbed or oscillatory WSS. These underlying conditions initiate intimal hyperplasia and stenosis, which can also lead to aneurysm formation.

Computational modeling has brought detailed mapping of WSS distribution and identified high-risk zones for potential stenosis. Described revelations affected surgical planning of AVF creation and have led to improvements for example in optimizing anastomosis angles for better flow geometry and cannulation techniques for hemodialysis.

Optimizing arteriovenous fistula performance requires thoroughly understanding how hemodynamic forces drive vascular remodeling. Recent progress in biomechanics and computational methods has clarified the role of shear stress, especially its disturbances, in both the maturation process and pathological outcomes. Joining biomechanical understanding with the best AVF design strategies and a correct clinical approach will ensure prolonged AVF functioning and a better life for ESRD patients.

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# Effect of Age, Practice Location and Covid-19 on the Use of POCT Methods by General Practitioners in Czechia in 2017–2021

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ABSTRACT
Background: Point-of-care testing (POCT) helps accelerate and streamline many processes in primary care. However, there is little information on the characteristics of their users.
Methods: Data were provided by the largest Czech health insurance company, covering 60% of the population. A proprietary spatial categorization model based on OECD typology, adapted to Czech primary care conditions, was used for localization.
Results: In all monitored groups, we observed continuous growth in the number of general practices using POCT methods, unaffected by Covid-19. Absolute numbers of POCT-INR and POCT-CRP examinations decreased during the pandemic years. The number of POCT-INR tests is more affected by practice location, while the number of POCT-CRP tests is influenced by the age of GPs.
Conclusions: Although POCT methods are a voluntary part of general practitioners' office equipment in Czechia, their more frequent use indicates that system-level conditions are appropriately set. The interest of GPs aged 60+ is surprising. Despite using POCT examinations the least, they show similar growth to other groups.

KEYWORDS
primary health care; general practice; rural health; covid-19; point-of-care systems

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## INTRODUCTION

This article follows our previous study describing the use of selected POCT methods by general physicians in Czechia (1). In it, we focused on the differences between urban and rural general practices. We analysed contractual data of the largest health insurance provider in Czechia (General Health Insurance Company, GHIC) from 2016. Czechia's healthcare system is characterised by low monetary participation of patients (2) who are not used to paying for the procedures covered by health insurance. Thus, the data provided by the GHIC is a suitable data source because the procedures performed are reported to the health insurer, which subsequently disburses them to the practices. However, we did not have data on the number of procedures performed available.

This study aims to follow the previous article by monitoring the trends in using selected POCT methods in time over five years (2017–2021). Besides the urban – rural dimension, we included the age of GPs in the monitoring, considering the potential differences in working habits in various age categories, particularly those of physicians in the retirement age (3, 4). Furthermore, the Covid-19 pandemic burst out during this period, so we could evaluate the trends in time using three criteria: the age of physicians, practice location, and the impact of Covid-19. We also newly had available the number of procedures performed.

The Covid-19 pandemic declared by the WHO in March 2020 (5) had a substantial impact on the way primary care was delivered worldwide (6, 7). Restricted visits to general practices were reflected in many activities carried out by GPs, including – concerning POCT methods – limited antibiotics prescriptions (8, 9) and a lower number of colorectal cancer screening tests (10). On the other hand, many activities have changed to a minimum extent, including prescriptions for medicines for chronic conditions (9) and care for diabetics (11). Thanks to the five-year interval chosen, we could evaluate three normal years (2017–2019) and two years affected by the pandemic (2020 and 2021)

Using POCT methods in primary care practices reflects the scope of tasks that GPs must perform – from treating infectious diseases over monitoring patients with chronic conditions (including cardiovascular diseases and diabetes) to preventive care. There are substantial differences between individual countries (12), which also applies to the Central European region (13, 14). It is associated with the different weights of primary care in individual healthcare systems (15). In the past, the weight of primary care in Czechia was evaluated as weak due to low competencies and funding (16). The POCT methods expand GPs' diagnostic and treatment options, provide measurable improvements in patient care, and increase cost-effectiveness (17).

GPs in Czechia use a wide array of POCT methods (18). The mandatory equipment of each general practice includes a glucometer and accessories for the chemical examination of urine. As for FIT, GPs can analyse the tests on their own devices or refer them to accredited laboratories. GPs have these procedures contracted automatically with all health insurance providers. Other procedures are performed voluntarily on the condition that the GP owns the device and secures the procedure's external quality control within one year (only INR requires completion of certified training evaluated with a test). The voluntary POCT methods GPs use includes INR, CRP, HbA1c, D-dimers, troponin T, and NT-pro BNP. Surgeries of paediatricians frequently use the detection of group A β-haemolytic Streptococcus (GABH). In their home environment, patients use pregnancy tests; patients with diabetes use glycemia self-monitoring, and the INR self-monitoring is gradually expanding, as well.

Using individual POCT methods follows the regularly updated and recommended procedures published by the professional society associating general practitioners (The Society of General Practice) (19). ECG was used as a reference procedure. This examination has historically been the most accessible for GPs and can be regarded as a suitable reference indicator in Czechia as far as voluntary surgery equipment is concerned.

## METHODS

We had available data from the largest health insurance provider in Czechia (GHIC) for the years 2017–2021. A total of 5.9 million people (including 4.5 million adults) were insured with the GHIC in the monitored period, i.e., about 60% of Czechia's population (20). Considering its nationwide activities, a contract with the GHIC is regarded as a standard, although the share of people insured by the GHIC differs in individual regions. Nonetheless, all general practices providing full-fledged treatment and preventive care have a contract with the GHIC.

In terms of the location, we categorised GP practices using our own model based on the regional typology principle according to the OECD (21), which we also used in many previous studies (1, 11, 22). This model categorises general practices into three types (Type 1 – urban, Type 2 – intermediate, Type 3 – rural) but is applied at a lower regional level that functionally corresponds to the primary healthcare structure in Czechia. While the OECD typology is built on the regional level NUTS 3, this modified typology uses the level of districts (LAU 1) and regions of municipalities with extended powers (MEP). In Czechia, it means smaller towns with a lower regional competence level in state administration. Another evaluation criterion is the presence of a hospital providing acute care in at least one essential field (internal medicine, surgery, paediatrics, gynaecology) in the given settlement. The intermediate type is divided into two subtypes: MEP with a hospital (Type 2a) and MEP without a hospital (Type 2b). If a provider runs several practices of multiple types, they are assigned to the type with a larger contracted share.

We also divided general practices into three groups based on the physicians' age. The limits were set at 40 and 60 years, i.e., the groups are as follows: "–39", "40–59", and "60+". In the case of multiple physicians with minimal FTEs, the resulting average age of physicians at the workplace is weighted according to the workload of each physician. Age categories were selected with regard to the minimum age of doctors upon completion of their curriculum (28 years), the average age of GPs in Czechia

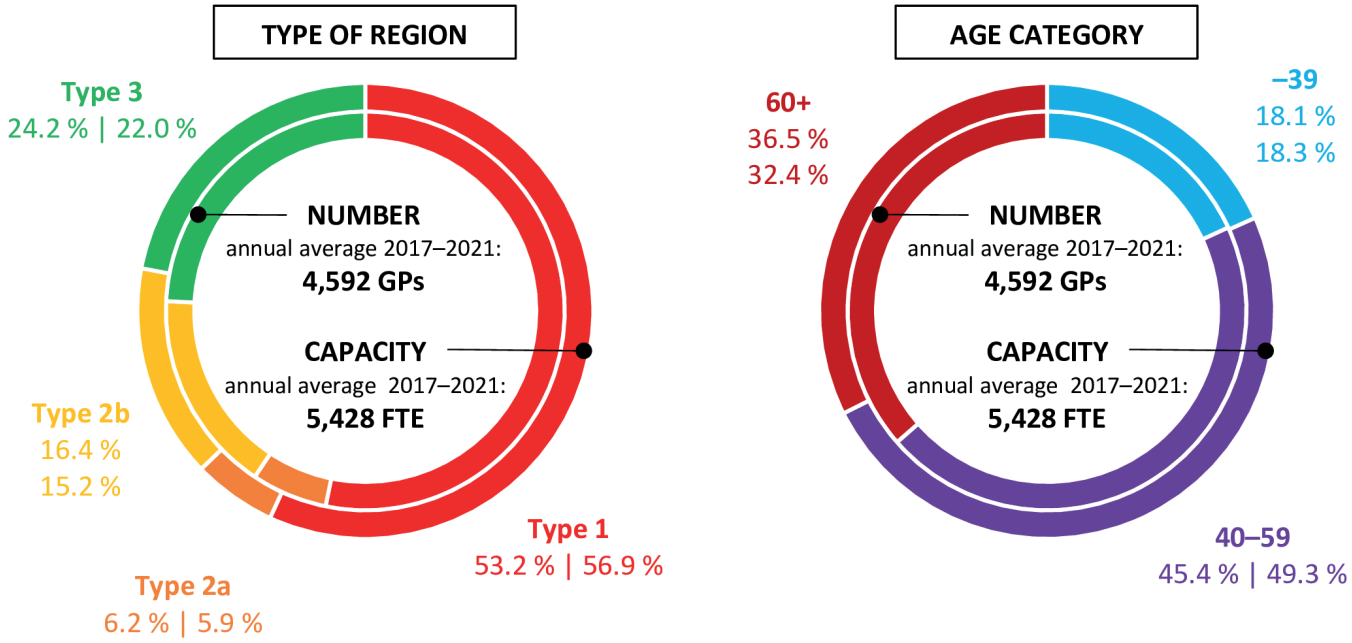


**Fig. 1** Percentage of GPs by type of region and age category, Czechia, 2021.
Source: GHIC.

(54.8 years), and a more than 40% share of GPs aged 60+ in the total FTE capacity in Czechia (22). Thus, this division reflects the representation of young doctors, doctors of retirement age and doctors of pre-retirement age in the system. The retirement age in Czechia is gradually increasing (legislation currently sets a cap on the retirement age at 65 years). Now it is around 64 years (e.g., men and women without children born in 1960 retire at the age of 64 years + 2 months, while women with three/four children retire at 60 years + 8 months). Thus, our defined group of 60+ includes doctors who have already retired or are expected to retire within five years. The total number of practices and the FTE capacity by individual groups are shown in Figure 1 (urban practices have a moderately higher capacity compared to rural surgeries, and the same applies to the 40–59 category compared to 60+).

We analysed the GHIC data from the contractual perspective (i.e., whether the general practice has the monitored POCT method covered by the contract), the procedural perspective (i.e., whether the surgery actually reports the contracted procedure, hence performs it), and from the quantitative perspective (the number of procedures in individual years, see Table 1). For greater transparency, we converted the number of examinations performed to the full-time equivalent (FTE). Subsequently, we compared the share of individual POCT methods in individual GP groups, separately and in concurrence. The monitored methods included POCT-INR, POCT-CRP, POCT-HbA1c, FIT – the analytical part, and ECG as a reference method.

## RESULTS

Table 1 shows the number and Figure 2 the share of individual POCT methods in the selected groups. The growing number of reporting practices is a clear trend across all methods and all GP groups. The pace of growth is about the same in terms of individual methods. The Covid-19 pandemic did not affect this trend at all. Doctors in the –39 group had the highest percentage share, followed by the age group of 40–59 and rural GPs. On the other hand, 60+ GPs had the lowest share, followed by urban GPs. While the scatter by age reached 15–20 percentage points, the dispersion by the location of practices was not that significant and increased by ten percentage points only in the case of POCT-INR.

**Tab. 1** Number of procedures of selected POCT methods by GPs in the period 2017–2021.

| POCT Method | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| INR | 604,532 | 662,984 | 709,074 | 668,182 | 574,761 |
| CRP | 455,615 | 562,980 | 659,773 | 488,353 | 555,808 |
| HbA1c | 35,239 | 40,798 | 50,138 | 56,726 | 73,101 |
| FIT | no data | no data | 116,653 | 270,090 | 310,409 |
| ECG | 533,649 | 582,038 | 665,371 | 641,813 | 750,808 |

Source: GHIC.

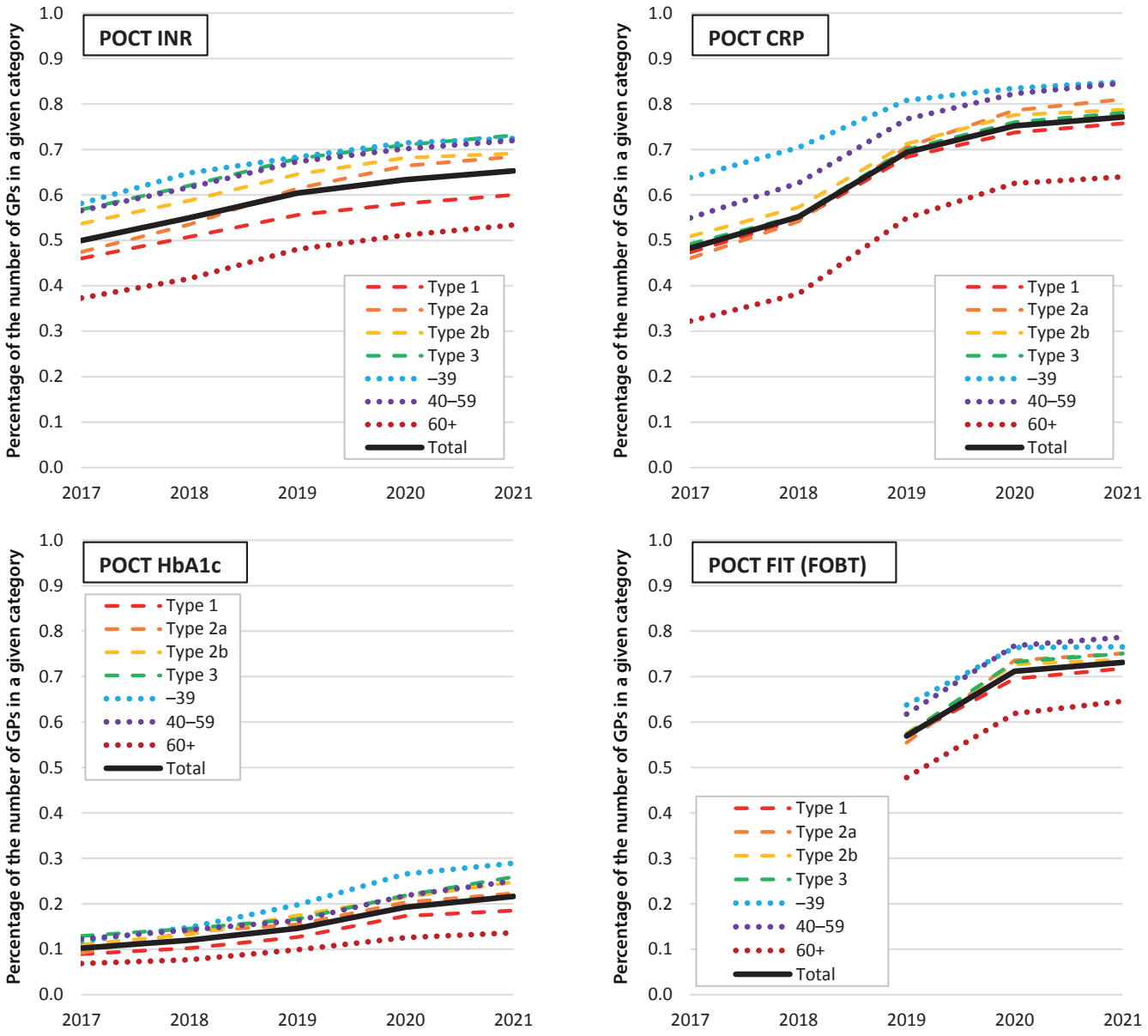


**Fig. 2** Use of selected POCT methods by GPs in the period 2017–2021.
Source: GHIC, authors' calculations.

POCT-CRP saw the highest increase during the five-year interval (28.8 p.p.). It was about half in the case of other methods (POCT-INR 15.3 p.p., FIT 16.2 p.p., POCT-HbA1c 11.4 p.p., reference ECG 12.1 p.p.). POCT-CRP gradually became the most used method (2021: 77.1% of practices), followed by FIT (73.1%). POCT-HbA1c was the least used method (21.6%). The reference procedure (ECG) was used in 66.5% of practices in the same period (Figure 3). The concurrence of the most widespread methods, POCT-CRP and POCT-INR, was 61.8% on average, with a five-year growth of 21.6 p.p. with the same distribution of groups as if individual methods were measured separately.

In 2021, 80.6% of surgeries (+20.9 p.p.) used at least one POCT method (without including the less used POCT-HbA1c), and its highest share was in the group of GPs aged 40–59 years. Additionally, it can be noted that the number of general practices not using a single POCT method dropped below 20% on average, with a highly vigorous dynamic exceeding 20 p.p. in the five-year interval (except for the group of –39 years where the share of such practices was the lowest in the long term and reached merely 13% in 2021). The reference procedure (ECG) also copied the growing use of POCT methods.

We saw different results in monitoring the number of examinations performed (Figure 4). While the rise in POCT-CRP and POCT-INR examinations in 2017–2019 was followed by a decline in the pandemic years 2020–2021, the number of POCT-HbA1c and FIT procedures had continuously increased. The shape of the curves related to individual methods was again identical in all monitored GP groups. Rural GPs performed the highest number of POCT-INR examinations, while urban GPs had the lowest share. In the case of POCT-INR procedures, the highest number was performed by doctors aged –39, while the lowest was performed by the 60+ age group. For POCT-HbA1c and FIT, the highest activity was seen among GPs of the intermediate type and rural GPs, while the lowest was recorded in the age group 60+ and urban GPs.

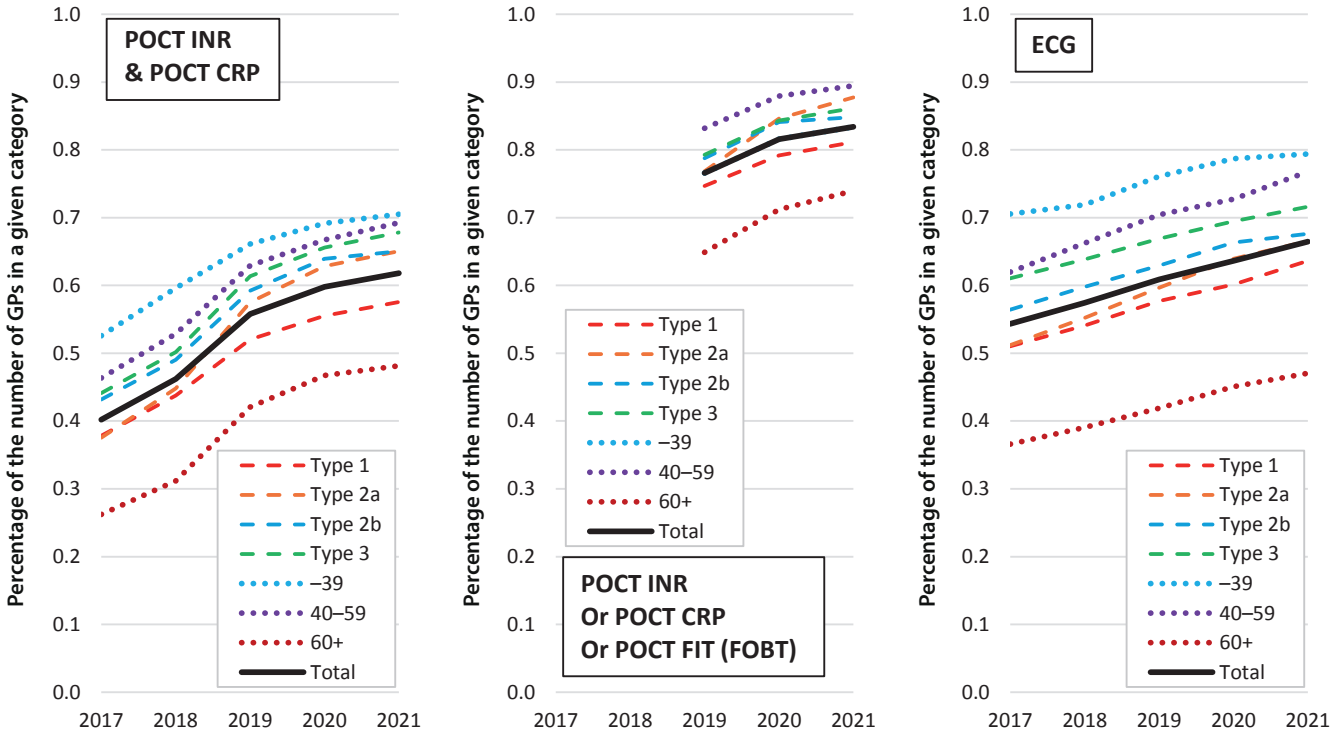


**Fig. 3** Simultaneous use of selected POCT methods by GPs and ECG use in the period 2017–2021.
Source: GHIC, authors' calculations.

## DISCUSSION

The GHIC is the largest health insurance provider in Czechia and is active throughout the country. Generally, its data can be regarded as sufficiently predicative thanks to its robustness. However, the general limitation includes an uneven share of people insured with the GHIC in various regions of Czechia. This limitation is relevant, particularly for quantitative indicators, i.e., the number of procedures performed in this case. However, as we do not compare specific regions in Czechia with different shares of people insured with the GHIC but homogenous groups of general practices defined by their geodemographic characteristics, we do not consider this limitation a methodological obstacle. As regards the monitored period, it can be noted that the GP network in Czechia was even and stable in time despite the current negative trends (22).

The differences in the number of POCT procedures between urban and rural practices were not proved abroad (23, 24). In Czechia, a single study was conducted using data from a small, regionally active health insurance company. It proved a rise in POCT procedures over time. However, spatial differences were not investigated, particularly with regard to the relatively small number of insured people and the specifically limited regional scope of this health insurance company for employees (25).

The continuous growth in the number of general practices using POCT methods testifies to the favourable setting of the contractual system of health insurance providers. Once a GP purchases a specific device, they must only register it and can report the procedure immediately with the respective code after their contract with the health insurer is amended. Periodical external quality inspections and submission of the relevant certificates are the only conditions. Differences regarding the preferences of individual GP groups can be seen in the number of procedures performed. The impact of the location is evident in the case of POCT-INR, where rural practices conduct about twice as many procedures as urban surgeries. With POCR-CRP, the same trend is apparent in age group comparisons (GPs in the group –39 carry out up to twice as many tests as GPs aged 60+).

Thus, this data confirms the findings proven globally, i.e., that GPs are increasingly interested in using POCT methods in their practices, especially those helping to diagnose acute conditions (26). The higher use of POCT-INR by rural GPs can be explained by their care for chronic patients treated with Warfarin, who are monitored in their practices, so they do not need to commute to specialist surgeries. The experience from abroad corresponds to this development, showing high patient satisfaction with using POCT-INR in general practices (27).

The most important aspect when purchasing a device is its beneficial effect and usefulness in clinical decision-making (28), which, however, probably differs in individual surveyed GP groups. This fact is demonstrated by the lower use of POCT-HbA1c, which can be affected by the wording of the recommended procedure (in uncomplicated patients with T2DM, HbA1c is routinely examined twice per year, but it is part of a complex laboratory examination once per year – GPs in Czechia are not apparently sufficiently motivated to buy the device due to the remaining one examination per year).

The colorectal cancer screening programme was launched in Czechia in 2000 (29) for people over 50. The most recent amendments took place in 2018 and 2019 from when only quantitative POCT with a fixed cut-off could be used (a condition for reporting an analytical procedure).

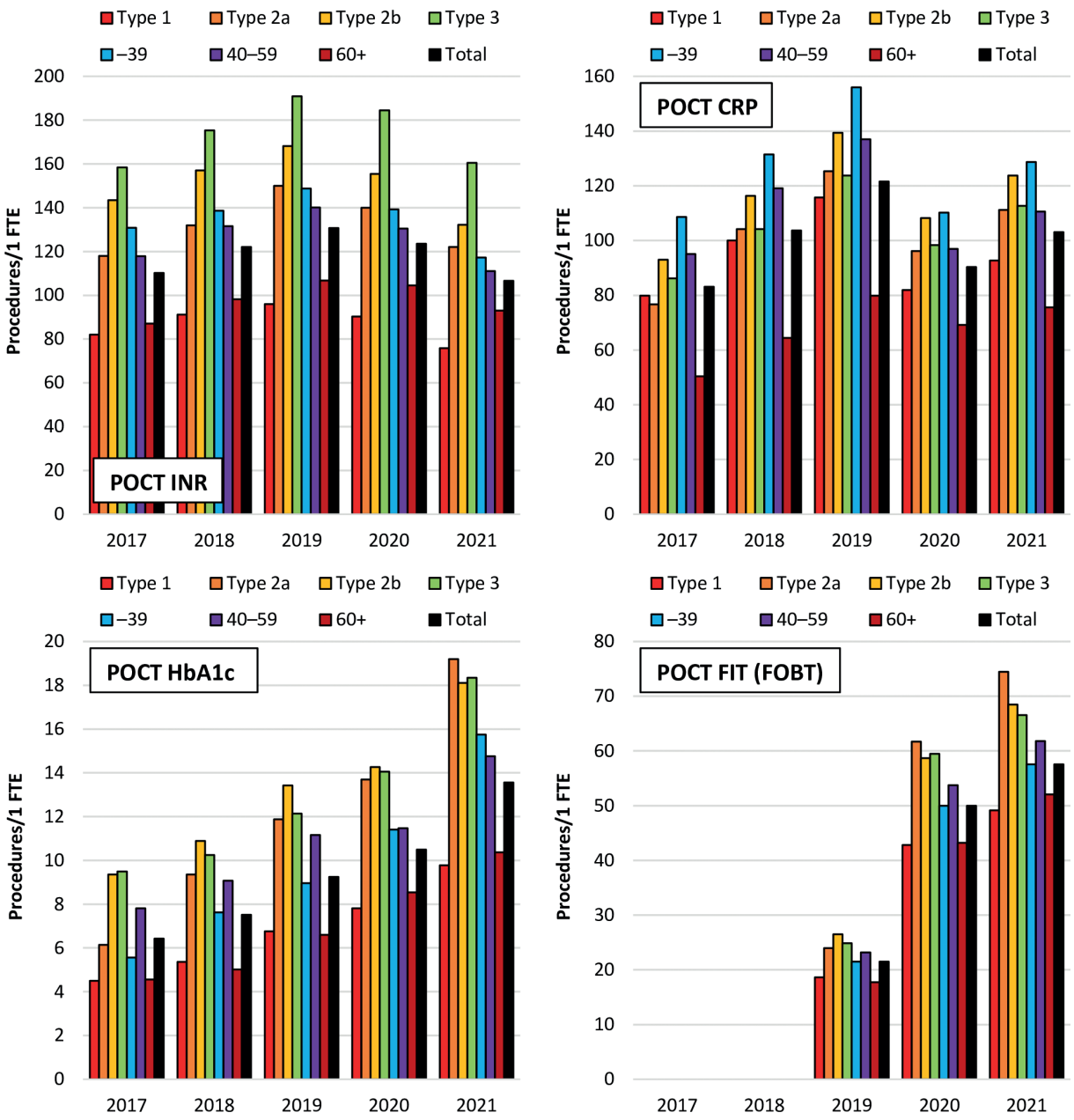


**Fig. 4** Number of selected POCT methods used by GPs in the period 2017–2021.
Source: GHIC, authors' calculations.

Therefore, we have data for this method from as late as 2019. Nevertheless, GPs can also refer stool samples to lab analyses if they do not have the respective device. That is why the number of analytical procedures in general practices differs from the total number of FIT tests conducted in the given year. In Czechia the COVID-19 pandemic had significantly negative impact on the total number of FIT examinations performed (11).

Similarly to 2016 (1), we detected a GP group in the following years who had contracted individual POCT methods but did not report them to health insurance providers. If we take individual procedures, it is about 2–7% of general practices, with POCT-HbA1c having the highest share. It is a surprising finding, considering the healthcare system conditions in Czechia, where it is not common to bill patients for POCT examinations. This phenomenon cannot be clearly explained, and the GPs are likely to bear the costs of buying and operating the respective equipment only to streamline administration for health insurance companies.

The market for medical devices in Czechia is highly competitive. GPs can choose from a wide array of devices, and dealers can advertise in specialised magazines and present their products at educational events for doctors. The offer includes both multipurpose devices that can perform multiple POCT methods and single-method devices. They also vary in size, which affects their potential portability outside surgeries to patient homes. The competitive environment applies also to external control and inspections. The price of POCT devices is comparable to the acquisition price of an ECG, which is why we also regard the use of ECG as a suitable reference indicator.

## CONCLUSIONS

The number of general practices using selected POCT methods in the monitored period 2017–2021 was continuously rising. Not even the Covid-19 pandemic put an end to the growing trend. We did not record differences in individual categories by age or practice location, yet the interest of the group 60+ is a surprise. Although they used POCT methods to the least extent, their trend curve has the same shape as that of other groups. The number of practices using multiple POCT methods also increased, as did those using at least one POCT method. That attests to the favourable setting of the contractual and disbursement conditions for using POCT methods in Czechia.

Concerning the number of examinations performed, we saw the highest differences by the practice location in the case of POCT-INR (a double use by rural practices compared to urban practices) and POCT-CRP (up to a double use by GPs aged –39 compared to the group 60+). This confirms the findings that the main motivation for buying a POCT device is its usefulness for clinical decision-making, which may, however, differ among individual groups.

The Covid-19 pandemic had a negative impact on the number of POCT-INR and POCT-CRP procedures performed. In contrast, it did not impact the growing number of POCT-HbA1c and FIT examinations (FIT concerned only a sample analysis in GP practices, not the total number of tests performed, which Covid-19 largely negatively affected). Still, we believe that the impact of Covid-19 on GPs using POCT methods in Czechia will be minimal in the long term. It is apparent from the continuously growing number of general practices reporting the respective procedures and identical shapes of the trend curves in individual GP groups.

## ABBREVIATIONS

| | |
|---|---|
| CRP | C reactive protein |
| ECG | electrocardiography |
| FIT | faecal immunochemical test |
| FTE | Full Time Equivalent |
| GABH | Group A β-haemolytic streptococcus |
| GHIC | General Health Insurance Company of the Czech Republic |
| GP | general practitioner |
| HbA1c | haemoglobin A1c |
| INR | international normalised ratio |
| LAU | Local administrative unit |
| MEP | municipalities with extended powers |
| NT-pro BNP | N-terminal type B natriuretic propeptide |
| NUTS | Nomenclature of units for territorial statistics |
| OECD | Organisation for Economic Co-operation and Development |
| POCT | point-of-care test |
| T2DM | type 2 diabetes mellitus |
| WHO | World Health Organization |

## CONFLICT OF INTEREST

We have no conflicts of interest to disclose.

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# Assessment of Urine Kidney Injury Molecule-1 as an Early Biomarker for Nephropathy in Sickle Cell Anaemia Patients

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## ABSTRACT

Background: Sickle cell anemia (SCA), a form of sickle cell disorder (SCD), is characterized by chronic hemolytic anemia, recurrent acute and persistent pain episodes, and progressive multiorgan complications. Among these, sickle cell nephropathy (SCN) is a significant and severe complication that may advance to chronic kidney disease (CKD), often beginning asymptomatically in childhood. Despite its clinical relevance, data on the early assessment of renal function in patients with SCA remain limited in Nigeria, hindering timely detection and intervention. This study, therefore, investigates the diagnostic utility of urinary kidney injury molecule-1 (KIM-1) as a biomarker for renal dysfunction in patients with steady-state SCA.

Objective: This study assessed urinary kidney injury molecule 1 as an early biomarker of nephropathy in patients with sickle cell anemia.

Method: This cross-sectional comparative study included ninety participants, comprising forty-five individuals with a normal hemoglobin genotype (HbAA) and forty-five with sickle cell anemia (HbSS). Hemoglobin genotype was determined using cellulose acetate electrophoresis. Serum creatinine levels were measured using the modified Jaffe method, and the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Urinary kidney injury molecule-1 (KIM-1) concentrations were assessed using the enzyme-linked immunosorbent assay (ELISA) technique.

Results: This study observed no significant difference in mean age between the HbAA and HbSS groups (14.16 ± 2.54 vs. 13.52 ± 3.33 years; $p = 0.121$). However, the mean body mass index (BMI) was significantly higher in the HbAA group (21.40 ± 1.02 kg/m²) compared to the HbSS group (18.69 ± 2.19 kg/m²; $p = 0.004$). Serum creatinine levels did not differ significantly between the two groups ($p = 0.311$). In contrast, urinary KIM-1 levels were significantly elevated in the HbSS group relative to the HbAA group ($p < 0.001$). In addition, a significant negative correlation was observed between urinary KIM-1 and estimated glomerular filtration rate (eGFR) in both groups, with the correlation being stronger in the HbSS group (HbAA: $r = -0.64$, $p = 0.005$; HbSS: $r = -0.79$, $p = 0.002$).

Conclusion: The findings from this study observed no significant difference in serum creatinine levels between individuals with HbAA and HbSS genotypes. However, urinary KIM-1 concentrations were significantly higher in the HbSS group, with a stronger negative correlation with eGFR. These findings suggest that, while serum creatinine may not be effective in detecting early renal impairment in sickle cell anemia, urinary KIM-1 has promising potential for detecting renal dysfunction in this population.

## KEYWORDS

nephropathy; sickle cell anaemia; urinary kidney injury molecule 1

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## INTRODUCTION

Sickle cell disorder (SCD) is an autosomal recessive hereditary hemoglobinopathy resulting from a point mutation in the β-globin gene, leading to the production of sickle hemoglobin (HbS) and associated with severe clinical manifestations (1). This mutation involves the substitution of valine for glutamic acid at the sixth position of the β-globin chain, located on the short arm of chromosome 11p15.5 (2). The most common HbS genotype is HbSS, accounting for approximately 69.9% of cases, followed by HbSC (27.2%) and sickle β-thalassemia (2.95%) (3–5). HbSS is characterized by chronic hemolytic anemia, recurrent episodes of severe pain, and progressive end-organ damage throughout life (6).

According to epidemiological studies, SCD predominantly affects individuals of African or Afro-Caribbean descent, with approximately 1 in 12 carrying the sickle cell trait and 1 in 365 Black infants in the United States diagnosed with SCD, accounting for an estimated 100,000 cases nationwide and millions globally (6). Of the approximately 300,000 infants born annually with SCD worldwide, 75% are born in sub-Saharan Africa. Sickle cell anemia (SCA), the homozygous form of SCD, represents the most common monogenic disorder in Africa. In Nigeria, the prevalence of homozygous SCD (HbSS) is estimated at 2–3%, with over 150,000 newborns affected each year (7).

The pathophysiology of SCD is driven by the presence of abnormal hemoglobin (HbS) within red blood cells, which leads to cellular deformation or "sickling" upon deoxygenation. The sickling of red blood cells results from a single nucleotide substitution (adenine to thymine) in the codon for the sixth amino acid of the β-globin gene. This mutation alters the normal glutamic acid codon (GAG) to a valine codon (GTG). Unlike glutamic acid, which is hydrophilic, valine is a hydrophobic amino acid, contributing to the abnormal polymerization of deoxygenated hemoglobin S and subsequent red cell sickling (8). These rigid, sickled cells obstruct the microvasculature, causing vaso-occlusion, which underlies the clinical symptoms and progressive organ damage characteristic of the disease (9).

SCN is a severe complication of SCA, characterized by early, often asymptomatic onset in childhood and a potential progression to chronic kidney disease (CKD) (7). SCN presents a significant challenge in the clinical management of patients with sickle cell anemia, contributing to a reduction in life expectancy by approximately 20 to 30 years. The clinical progression of SCN is age-dependent, with renal dysfunction typically emerging during childhood and gradually advancing to chronic kidney disease and, ultimately, kidney failure by the third or fourth decade of life (10).

Despite its clinical significance, limited research has evaluated renal function in young Nigerian patients with SCA, hindering early detection and timely intervention to reduce associated morbidity and mortality. This study, therefore, investigated the diagnostic utility of urinary KIM-1 as a biomarker for renal dysfunction in individuals with steady-state SCA.

## MATERIALS AND METHODS

### STUDY DESIGN

This cross-sectional comparative study was carried out to assess the diagnostic value of KIM-1 as an early biomarker to identify tubular nephropathy in sickle cell patients (HbSS) and age-matched non-sickle cell individuals (HbAA).

### ETHICAL APPROVAL

This study was approved by the Institutional Review Board of General Hospital, Ilorin, Kwara State, Nigeria, with reference number GHI/ADM/134/VOL.II/387 prior to its commencement. The detailed information regarding the study's objectives, potential benefits, risks, and the autonomy to partake was thoroughly explained to the participants. Also, detailed information about this study was equally explained to the children based on their level of understanding and to their parents and guardians to obtain their explicit and implied consent. In accordance with the Declaration of Helsinki (11), each participant provided verbal and written informed consent prior to the commencement of the study.

### SAMPLING TECHNIQUE

Following the detailed explanation of this study to the prospective participants, their informed consent was obtained. Each prospective participant was instructed to aseptically produce a clean-catch spot urine sample that was screened for overt proteinuria to qualify their participation. Those who were qualified were recruited into the study consecutively by convenient random sampling. Sociodemographic information was gathered from the participants using a semi-structured questionnaire. With light clothing and shoes off, each participant's height and weight were recorded to the closest 0.1 m (m) and kilogram (kg), respectively, using a standardized, accurately calibrated Europharma Stadiometer with a weighing scale (measuring station).

### INCLUSION CRITERIA

i. Stable-state SCA patients (HbSS) and age-matched non-sickle cell individuals (HbAA) attending General Hospital Ilorin.
ii. Individuals who consented to the study or whose parents/guardians did so.
iii. Individuals without overt proteinuria screened by urinary dipstick technology.

### EXCLUSION CRITERIA

i. Individuals who were screened to have overt proteinuria with urine dipstick technology.
ii. Individuals diagnosed with end-stage kidney disease.

### SAMPLE COLLECTION AND PROCESSING

Five (5) milliliters of blood samples were collected from each study participant following an aseptic procedure and

dispensed into gel activator bottles. They were packed securely and delivered to the laboratory for processing and analysis. The blood samples were allowed to clot and spun at 3,000 rpm for 5 minutes using a TDL-24 bench-top laboratory centrifuge. Following the centrifugation, the sera were then transferred into sterile plain tubes.

Aliquots of urine samples from participants who were screened negative for overt proteinuria using urine dipstick technology were also transferred into plain tubes for urinary creatinine and kidney injury molecule 1 estimation.

Every participant's sample bottles were appropriately labeled using the same code. All samples were analyzed in duplicate.

## LABORATORY ANALYSIS

### QUALITATIVE DETERMINATION OF URINARY PROTEINURIA

The qualitative determination of urinary proteinuria was carried out by dipstick technology of Cortez Diagnostics, Inc., urinary protein strips (12) as a screening tool for exclusion. Participants without overt proteinuria were included in the study, while those with overt proteinuria were excluded from the study. The test was based on the "protein error" principle of indicators. When pH is held constant by a buffer, indicator dyes release $H^+$ ions because of the protein present and change color from yellow to blue-green.

### DETERMINATION OF HAEMOGLOBIN GENOTYPE

The hemoglobin genotype was ascertained using the DY-300 Electrophoresis Machine based on the principle of the cellulose acetate electrophoresis separation technique, which was modified by (13). A cellulose acetate membrane or strip serves as a support matrix in cellulose acetate electrophoresis, which separates the hemoglobin components in a sample. An electrophoresis running buffer, kept at a pH of 6.8, is placed inside the electrophoresis tank, submerging the cellulose acetate membrane that has the hemolyzed blood sample and standard controls applied to it. After the machine is turned on, the separation process lasts for 15 minutes. Components of the sample are separated into discrete bands or zones upon completion of the separation process. The hemoglobin genotype in each band is represented by the samples' traits that are either the same as or comparable to those of the controls.

### QUALITATIVE ESTIMATION OF SERUM CREATININE

The serum creatinine was quantitatively measured using the creatinine assay kits from ESB Biomedicals, Nigeria, based on the modified Jaffe's colorimetric method (14). The assay was based on the reaction of creatinine with sodium picrate. Creatinine reacts with alkaline picrate, forming a red Janovski complex. The time interval chosen for measurements avoids interference from other serum constituents. The intensity of the color formed is proportional to the creatinine concentration in the sample measured at 520 nm spectrophotometrically.

### ESTIMATION OF GLOMERULAR FILTRATION RATE (EGFR)

The CKD-EPI Equation 2021 (15) was used to estimate the glomerular filtration rate (eGFR), which was used to measure kidney function.

$$eGFR = 142 \times \min(Creat/K, 1)^{\alpha} \times \max(Creat/K, 1)^{-1.200} \times 0.9938^{age} \times 1.012 \text{ (if female)}$$

where $K = 0.7$ (female) or 0.9 (male) and $\alpha = -0.241$ (female) or $-0.302$ (male)

### QUANTITATIVE ESTIMATION OF URINARY KIDNEY INJURY MOLECULE-1 (KIM-1)

The enzyme-linked immunoassay (ELISA) method, as described by Jin et al. (16), was used to quantitatively estimate the urinary KIM-1 using the Sun Red (Shanghai, China) kit.

### DATA ANALYSIS

Statistical Package for Social Sciences (SPSS) version 20.0 software was used to analyze the data. Mean ± standard deviation was used to present the measured (serum creatinine and urine KIM-1) and sociodemographic (age, weight, height, and BMI) data. The mean variables between HbAA and HbSS were compared using an independent t-test. The Spearman correlation coefficient was used to evaluate the relationship between urinary KIM-1 and eGFR. Statistical significance was set at $p < 0.05$.

**Tab. 1** Sociodemographic Distribution of the Study Population.

| Parameters | HbAA (n = 45) Mean ± SD | HbSS (n = 45) Mean ± SD | t-value | p-value |
|---|---|---|---|---|
| Age (years) | 14.16 ± 2.54 | 13.52 ± 3.33 | 2.303 | 0.121 |
| Weight (Kg) | 42.55 ± 2.62 | 26.02 ± 4.01 | 0.123 | 0.000* |
| Height (m) | 1.41 ± 0.22 | 1.18 ± 0.12 | 0.247 | 0.002* |
| Body Mass Index (kg/m²) | 21.40 ± 1.02 | 18.69 ± 2.19 | 0.411 | 0.004* |

kg: kilogram, m: meter, kg/m²: kilogram per meter square, t-value: statistical measure to determine the difference between two means, *sig: $p < 0.05$.

## RESULTS

### SOCIODEMOGRAPHIC DISTRIBUTION OF THE STUDY POPULATION

The study participants' sociodemographic distribution is presented in Table 1, which also compares the means of four parameters (age, height, weight, and BMI) between those with the HbAA and HbSS genotypes statistically. The HbAA group had a slightly higher mean age (14.16 ± 2.54 years) than the HbSS group (13.52 ± 3.33 years). This difference, however, was not statistically significant (p = 0.121), suggesting that age is similar in the two groups and unlikely to have an impact on other outcomes that were measured. However, the mean weight of individuals with the HbAA genotype was 42.55 ± 2.62 kg, which was significantly higher (p = 0.000) than the mean weight of individuals with the HbSS genotype, which was 26.02 ± 4.01 kg. Similarly, the mean height of 1.41 ± 0.22 m for those with the HbAA genotype was significantly higher than the mean height of 1.18 ± 0.12 m for those with the HbSS genotype (p = 0.002). The mean BMI of the HbAA genotype participants was 21.40 ± 1.02 kg/m², which was significantly higher than the BMI of the HbSS group, which was 18.69 ± 2.19 kg/m² (p = 0.004).

### COMPARISON OF THE SERUM CREATININE AND URINARY KIM-1 OF STUDY PARTICIPANTS

Table 2 compares the levels of serum creatinine and urine Kidney Injury Molecule-1 (KIM-1) in participants with normal hemoglobin (HbAA) and sickle cell anemia (HbSS). Although the two groups' serum creatinine levels did not differ significantly (p = 0.311), the HbSS group's mean urinary KIM-1 levels were significantly higher (p = 0.000) than those of the HbAA group.

### RELATIONSHIP BETWEEN URINARY KIM-1 AND EGFR OF THE STUDY POPULATION

Table 3 presents the analysis of the relationship between urinary KIM-1 levels and eGFR, which revealed significant negative correlations in both the HbAA and HbSS groups. In the HbAA group, the mean KIM-1 level was 2.44 ± 0.431, and the mean eGFR was 103.52 ± 16.125. The correlation coefficient (r = −0.64, p = 0.005) indicates a significant moderate negative correlation between KIM-1 and eGFR, suggesting that as KIM-1 levels increase, eGFR decreases significantly in this group. In the HbSS group, KIM-1 levels were higher, with a mean of 3.11 ± 0.222, and eGFR was lower, with a mean of 92.54 ± 17.272. The negative correlation was significantly stronger in this group, with a correlation coefficient (r = −0.79, p = 0.002). This strong negative correlation suggests that the increase in KIM-1 levels is associated with a more pronounced decrease in eGFR among individuals with HbSS.

## DISCUSSION

SCA is a rare genetic blood condition affecting millions worldwide. Renal complications are common in both adult and pediatric SCA patients, and they pose a serious risk of increasing mortality. Effective renal plasma flow and glomerular filtration rates are higher in young SCD patients but decrease to normal ranges and subnormal levels in young adulthood with advancing age (17, 18). In the SCD population, the prevalence of kidney failure varies between 5 and 18% (10). Nonetheless, 16–27% of the pediatric population has CKD, according to Kidney Disease Improving Global Outcome (KDIGO) criteria (19). KIM-1, a type I transmembrane glycoprotein, is undetectable in normal kidneys, and its level increases in urine as a result of nephrotoxic injury of proximal tubule cells after 12–24 h (20).

As an early biomarker of renal dysfunction, we evaluated the clinical utility of kidney injury molecule-1 (KIM-1) to detect early indicators of renal damage in sickle cell patients prior to the development of overt nephropathy.

In this study, we recruited 90 participants consisting of 45 HbAA participants (age: 14.16 ± 2.54 years, weight: 42.55 ± 2.62 kg, height: 1.41 ± 0.22 m, BMI: 21.40 ± 1.02 kg/m²) and 45 HbSS (age: 13.52 ± 3.33 years, weight: 26.02 ± 4.01 kg, height: 1.18 ± 0.12 m, BMI: 18.69 ± 2.19 kg/m²). Table 1 compares sociodemographic characteristics between HbAA and HbSS genotype

**Tab. 2** Comparison of Serum Creatinine and Urinary KIM-1 of the Study Participants.

| Parameters | HbAA | HbSS | t-test | p-value |
|---|---|---|---|---|
| SCr (mg/dl) | 0.868 ± 0.093 | 0.848 ± 0.096 | 1.019 | 0.311 |
| Urinary KIM-1 (ng/ml) | 2.440 ± 0.431 | 3.110 ± 0.222 | 3.741 | 0.000* |

SCr: serum creatinine, mg/dl: milligram per deciliter; Urinary KIM-1: urinary kidney injury molecule, ng/ml: nanogram per milliliter, *sig = p < 0.05.

**Tab. 3** Relationship Between KIM and eGFR in the Study Population.

| Group | Urinary KIM-1 (ng/ml) | eGFR (ml/min/1.73m²) | n | r-value | p-value |
|---|---|---|---|---|---|
| HbAA | 2.44 ± 0.431 | 103.52 ± 16.125 | 45 | −0.64 | 0.005* |
| HbSS | 3.11 ± 0.222 | 92.54 ± 17.272 | 45 | −0.79 | 0.002* |

Urinary KIM-1: Urinary Kidney Injury Molecule-1, ng/ml: nanogram per milliliters, eGFR: estimated Glomerular Filtration Rate, ml/min/1.73m²: milliliters per minute per 1.73 squared meters, n: number of participants, r-value: Correlation coefficient, *sig = p < 0.05.

participants. While there was a slight difference in age between the two groups (14.16 ± 2.54 years for HbAA versus 13.52 ± 3.33 years for HbSS), this difference was not statistically significant ($p = 0.121$). This suggests that age did not significantly influence the observed differences between the two groups. In contrast to age, the two groups observed statistically significant differences in weight, height, and BMI ($p < 0.05$ for all comparisons). HbSS participants had significantly lower weight, height, and BMI compared to HbAA participants. The significantly lower weight, height, and body mass index (BMI) observed in HbSS participants compared to their HbAA counterparts might be due to the chronic disease burden and metabolic demands associated with SCA. Individuals with SCA often experience impaired growth and delayed physical development due to a combination of factors, including chronic hemolytic anemia, increased energy expenditure, recurrent vaso-occlusive crises, and suboptimal nutrient utilization. These factors can compromise nutritional status and hinder normal growth trajectories, particularly during critical developmental periods such as childhood and adolescence. These findings are consistent with a previous study by Martins et al. (21) and Rinam et al. (22) that reported delayed physical and sexual development in individuals with SCD, indicating a peripheral cause of hypogonadism, most likely brought on by androgen resistance in SCD patients. These findings underscore the necessity for comprehensive care strategies, including nutritional support and regular growth monitoring, to address growth and developmental challenges in patients with SCA.

Serum creatinine and urinary KIM-1 levels in HbAA and HbSS participants are compared in Table 2. There was no statistically significant difference in the serum creatinine levels of HbAA (0.868 ± 0.093 mg/dL) and HbSS (0.848 ± 0.096 mg/dL) between the two groups ($p = 0.311$). This implies that the levels of conventional indicators of kidney function were similar in the two groups. In sickle cell anemia, glomerular damage is the main cause of renal injury; however, not all patients experience sickle nephropathy at a young age. The need for early biomarkers to predict renal damage and direct prompt intervention is highlighted by the fact that traditional renal parameters, such as creatinine, frequently become abnormal late in the course of the disease. This result is consistent with Tehseen et al. (23), who reported that renal damage is a progressive complication of SCD that starts in childhood and can lead to renal failure and early death in 12% of adults with SCA. Also, it aligns with recent research indicating that standard renal biomarkers, such as serum creatinine, can underestimate kidney dysfunction in SCA patients due to factors like increased tubular secretion and reduced muscle mass, which lower creatinine production and mask early renal impairment (24).

Urinary KIM-1 levels were significantly higher ($p < 0.001$) in HbSS participants (3.11 ± 0.222) than in HbAA participants (2.44 ± 0.431), in contrast to serum creatinine. This underscores the potential of KIM-1 as a biomarker for early renal dysfunction in SCA and emphasizes the limitations of traditional renal markers like serum creatinine, which may not detect early kidney injury in SCA patients due to factors such as increased tubular secretion and reduced muscle mass. This finding is consistent with previous studies (25, 26) that reported KIM-1 as an early biomarker of renal tubular dysfunction in patients with SCD, often occurring prior to significant alterations in glomerular filtration rate. Also, this elevation indicates proximal tubular injury, reinforcing the role of KIM-1 as an early marker of renal damage in SCA (27). These findings suggest urinary KIM-1 is a promising biomarker for the early detection of renal dysfunction in SCA patients, potentially allowing for timely interventions to mitigate progression to chronic kidney disease.

The relationship between estimated glomerular filtration rate (eGFR) and urinary kidney injury molecule-1 (KIM-1) in participants with HbAA and HbSS genotypes is presented in Table 3. A statistically significant negative correlation ($p < 0.05$) was observed between KIM-1 and eGFR in both groups, with a significantly stronger negative relationship observed among individuals with SCA. Moreover, the mean eGFR was significantly lower in the HbSS group compared to the HbAA group, although only a small subset of HbSS participants exhibited an eGFR below 60 mL/min/1.73 $m^2$. These findings suggest a trend in which increasing urinary KIM-1 levels are associated with declining eGFR, highlighting the potential of KIM-1 as an early biomarker of renal dysfunction.

A study by Niss et al. (28) found that urinary KIM-1 levels were associated with baseline and persistent albuminuria, reinforcing its role as a marker of tubular injury in SCA. Similarly, this observation is consistent with the research by Kasztan et al. (29) in a mouse model of SCA revealed that increased urinary KIM-1 levels occurred early in the disease course, preceding significant declines in eGFR. Markers of tubular damage, including increased urinary KIM-1 excretion, interstitial fibrosis, and brush border loss, occurred before glomerular injury. Their findings also revealed that the severity of long-term renal damage in male HbSS mice was closely associated with the degree of hyperfiltration, suggesting a tubuloglomerular mechanism underlying early kidney injury. Based on the findings from this study, it is suggestive that urinary KIM-1 is a potential earlier biomarker for the detection of SCN.

## CONCLUSION

The findings from this study observed no significant difference in serum creatinine levels between individuals with HbAA and HbSS genotypes. However, urinary KIM-1 concentrations were significantly higher in the HbSS group, with a stronger negative correlation with eGFR. These findings suggest that, while serum creatinine may not be effective in detecting early renal impairment in sickle cell anemia, urinary KIM-1 has promising potential for early detection of renal dysfunction in sickle cell anemia patients.

## IMPLICATIONS FOR CLINICAL PRACTICE

Based on the findings from this study, urinary KIM-1 can serve as a non-invasive monitoring tool for renal function

in patients with SCA compared to conventional markers like serum creatinine.

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# Long-Term Outcomes and Survival of Peritoneal Dialysis Beyond 10 Years: A Single-Center Study

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ABSTRACT

Introduction: Long-term peritoneal dialysis (PD) beyond 10 years is uncommon and reflects both advances in dialysis care and the complexity of long-term patient management. The objective of this study is to describe the clinical characteristics, complications, and outcomes of patients undergoing peritoneal dialysis for more than 10 years, and to identify factors associated with long-term technique survival.

Methods: This is a retrospective, descriptive, and analytical study including 12 patients treated with peritoneal dialysis (PD) for more than 10 years between June 2006 and January 2024. Data collected included demographics, comorbidities, dialysis parameters, complications, and outcomes.

Results: The mean age at PD initiation was 45.5 ± 16.5 years. Tubulointerstitial nephropathy was the most common etiology of end-stage kidney disease. The mean duration on PD was 10.4 ± 0.9 years. During follow-up, residual kidney function significantly declined. Seven patients remained on PD at last follow-up. The peritonitis rate was low (0.024 episodes/patient-month), with favorable technique survival and no cases of encapsulating peritoneal sclerosis.

Discussion: PD beyond 10 years is feasible with proper patient selection, education, and follow-up. Preservation of residual kidney function and effective management of complications are key to long-term success, especially in non-transplantable patients.

KEYWORDS

peritoneal dialysis; 10 years; mortality; hemodialysis

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## INTRODUCTION

Few patients with kidney failure remain on peritoneal dialysis (PD) for 10 years or more. The clinical outcomes of patients on PD depend on many factors, including age, presence of comorbidities, nutritional status, and the properties of the peritoneal membrane.

Few studies report a peritoneal dialysis survival of more than 10 years. Prolonged survival on PD reflects advances in treatment techniques but also presents significant challenges.

The objective of this study is to describe the demographic and progressive characteristics of patients on PD for more than 10 years.

## MATERIAL AND METHODS

### STUDY POPULATION AND DESIGN

Our study included 12 patients on peritoneal dialysis (PD) for more than 10 years due to end-stage chronic kidney disease (ESKD) in our PD unit between June 2006 and January 2024.

The patients' age, sex, body mass index (BMI), socioeconomic status, as well as sociodemographic characteristics (such as the presence of a person assisting with PD exchanges), and the indication for PD were examined from their medical records.

The duration of PD, as well as the presence of a history of hemodialysis (HD) or kidney transplantation before starting PD, were recorded.

Comorbidities such as cardiovascular diseases, hypertension, and diabetes were noted.

### CLINICAL AND LABORATORY PARAMETERS

Measures of systolic and diastolic blood pressure, daily urine output, average daily ultrafiltration quantities as well as renal kidney function (RKF) for all patients were recorded at the start and during the final consultation. Serum values of urea, creatinine, calcium, phosphate, albumin, intact parathyroid hormone (iPTH), hemoglobin, and ferritin were obtained at the start of treatment and during the last follow-up.

The start of treatment for continuous ambulatory peritoneal dialysis (CAPD) was defined as the time after catheter placement and patient education, when they began using the standard 2 L four times per day CAPD regimen. The start of treatment for automated peritoneal dialysis (APD) was defined as the time when patients began PD with the required exchange volume, approximately 2 to 3 weeks after catheter placement.

We used a standard solution containing: 132 meq/L sodium, 3.5 meq/L calcium, 1.5 meq/L magnesium, 35 meq/L lactate,102 meq/L chloride. Glucose concentrations were adjusted according to the patient's volume status and intra-abdominal pressure (IPP).

Total daily clearance (peritoneal plus residual kidney) of peritoneal urea (Kt/V) and weekly creatinine clearance (WCC) were measured, along with a peritoneal equilibrium test (PET) during PD treatment. Body mass index (BMI) was defined as the body weight divided by the square of the individual's height.

### DEFINITIONS OF COMPLICATIONS

Infections were classified as follows:

Exit site infections (defined by drainage, erythema, or pain at the exit site),

Tunnel infections (defined by swelling, pain, or tenderness with or without erythema over the catheter tunnel).

Peritonitis was defined by the presence of cloudy effluent with 100 white blood cells/L, of which 50% were neutrophils according to the ISPD guidelines (1).

Mechanical complications were recorded throughout the duration of peritoneal dialysis and classified according to ISPD guidelines as catheter migration, catheter dysfunction, catheter perforation, and peritoneal leaks. Catheter migration was defined as displacement of the catheter tip from the pelvic cavity, resulting in impaired dialysate inflow or outflow, potentially requiring conservative maneuvers or surgical intervention. Catheter dysfunction was defined as impaired inflow or outflow due to tip malposition, obstruction by fibrin, omentum, blood clots, or kinking, necessitating medical or surgical management such as repositioning, fibrinolytic therapy, or catheter replacement. Peritoneal leaks were defined as the escape of dialysate into subcutaneous tissue, pleura, or other compartments, diagnosed clinically or radiologically, often requiring temporary cessation of PD, reduction of dwell volumes, or catheter management. The relationship between mechanical complications and the duration of PD was also evaluated.

Factors associated with mortality were analyzed for all patients. Patient survival rates were calculated from the start of PD treatment until the end of PD therapy or until the end of follow-up (January 1, 2024).

### PATIENT SELECTION AND TRAINING

Before initiating peritoneal dialysis, patient eligibility was carefully evaluated. In addition to the patient's preference, selection criteria included adequate cognitive and functional ability to perform exchanges correctly, absence of major abdominal surgery or hernias, satisfactory home hygiene conditions, and, when necessary, the availability of a caregiver.

All patients and their caregivers participated in a standardized training program conducted by specialized PD nurses. This program lasted an average of 5 to 7 days and combined theoretical and practical sessions on hand hygiene, mask use, exit-site care, preparation of exchange materials, and aseptic exchange techniques. Training was reinforced through visual demonstrations and supervised exchanges until full autonomy was achieved.

Patients were clinically and biologically assessed after 15 days, at one month, and then every three months during routine follow-up visits. Retraining sessions were organized every 6 to 12 months or after any infectious episode to reinforce proper technique. Home visits and periodic audits were also performed to ensure adherence to hygiene and exchange procedures.

Written and visual educational materials were provided in Arabic and French to standardize training and ensure comprehension. These included posters and wall displays within the PD unit, illustrated flyers summarizing key steps of exchange procedures, slide presentations used during training sessions, and therapeutic education courses designed to reinforce adherence and infection prevention practices.

### ETHICS STATEMENT

Informed consent has been obtained, that studies have been performed according to the Declaration of Helsinki, and that the procedures have been approved by the local ethics committee.

### STATISTICAL ANALYSIS

All quantitative variables were expressed either as mean ± standard deviation or as median with interquartile range, while qualitative variables were expressed as number (percentage). Student's t-tests and ANOVA were performed to determine differences between groups. A binomial test or chi-square test was used for the comparison of qualitative data. A p-value of <0.05 was considered statistically significant. Data management and analysis were performed using Jamovi software version 2.3.21.

**Tab. 1** Demographic Characteristics of the Patients.

| Patients' Characteristics | | Results (n = 12) |
|---|---|---|
| Autonomy | | 10 (83.5%) |
| Indication for peritoneal dialysis<br>Choice/Vascular access exhaustion | | 11 (91%)<br>/1 (9%) |
| Good socio-economic status | | 9 (75%) |
| Education level | Higher education<br>High school<br>Primary school<br>Illiterate | 9 (75%)<br>1 (9%)<br>1 (9%)<br>1 (9%) |
| Professional activity | Medical Doctor<br>Engineer<br>Retired<br>Nurse<br>Other | 1 (9%)<br>2 (18%)<br>3 (27%)<br>1 (9%)<br>6 (50%) |
| Hemodialysis before PD<br>Duration of hemodialysis (months) | | 3 (27%)<br>48 [36–60] |
| Transplantation before DP<br>Duration of transplantation (months) | | 2 (18%)<br>72 [60–84] |
| Initial Nephropathy | Tubulo-interstitial<br>Polycystic Kidney Disease (PKD)<br>Nephrosclerosis (NAS)<br>Indeterminate | 4 (33.5%)<br>1 (9%)<br>3 (27%)<br>4 (33.5%) |
| Transfer to Automated Peritoneal Dialysis (APD)<br>Duration of the initial technique (CAPD or APD) (months) | | 5 (41.7%)<br>69 [48–91] |
| PET | Fast transporter<br>Slow transporter | 5 (33.5%)<br>3 (27%) |

## RESULTS

### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Since the establishment of our peritoneal dialysis unit in June 2006 and until January 2024, 235 patients have been recruited. Twelve of these patients, who have remained on peritoneal dialysis (PD) for more than 10 years, were included in the study, representing 5% of the recruited patients.

Among patients who remained on peritoneal dialysis for more than 10 years, the average age at initiation of PD was 45.5 ± 16.5 years, with an age range from 16 to 71 years, 58% were female and 42% were male, yielding a male-to-female ratio of 0.72. The mean body mass index (BMI) was 27.5 ± 4.5 kg/m².

Tubulointerstitial nephropathy was the most common cause of end-stage kidney disease (33.3%), followed by nephrosclerosis (25%).

Two patients had previously received a kidney transplant; one of them lost the graft 7 years after transplantation due to graft sepsis and started peritoneal dialysis 1 year later, while the other had the failed graft left in situ.

Ten patients are hypertensive, one patient is diabetic. Ischemic heart disease was found in two patients, and the median Charlson comorbidity score was 2. None of the patients had a history of hernia.

Only one patient started with automated peritoneal dialysis (APD), while 5 patients out of the 11 initially on continuous ambulatory peritoneal dialysis (CAPD) switched to APD due to loss of ultrafiltration. The demographic data are summarized in Table 1.

### CLINICAL AND BIOLOGICAL OUTCOME

After 10 years on PD (T1), no significant changes were found in blood pressure (131/69 mmHg compared to 129/75 mmHg) or BMI (28.5 kg/m² compared to 27.6 kg/m²) ($p > 0.05$). Urine output decreased significantly from 1500 [1000–2000] mL/day to 0 [0–150] mL/day ($p = 0.010$), and residual kidney function declined from 4.6 [1.44–7.7] mL/min to 0 [0–1.14] mL/min ($p = 0.001$). Ultrafiltration increased from 400 [178–600] mL/day to 1000 [900–1500] mL/day ($p < 0.001$). Only one patient was anuric at PD initiation, and residual kidney function became null in 2 patients after 5 years of PD, while two patients still maintained a residual kidney function more than 4 mL/min at 10 years.

Clearance parameters showed a decline, with Kt/V changing from 1.56 ± 0.6 to 1.41 ± 0.48 ($p = 0.800$) and weekly creatinine clearance decreasing from 92.4 ± 43.5 to 49 ± 21 mL/min ($p = 0.010$). Bicarbonate levels dropped significantly from 26.6 ± 2.07 to 17.9 ± 3.7 mmol/L ($p < 0.001$) (Table 2).

Nutritional parameters showed a decrease in normalized protein catabolic rate (nPCR, 0.766 ± 0.21 to 0.615 ± 0.09 g/kg/day, $p = 0.08$), albumin (38.2 ± 6.08 to 37.1 ± 5.65 g/L, $p = 0.777$), and triglycerides (1.93 ± 1.03 to 1.69 ± 0.85 g/L, $p = 0.633$). Hemoglobin improved from 10.6 ± 2.07 to 11.1 ± 1.65 g/dL ($p = 0.032$) with erythropoietin and iron supplementation.

Calcium levels increased from 79.7 ± 13 to 91 ± 8 mg/L ($p = 0.033$), along with phosphate levels, despite the use of

**Tab. 2** Evolutionary Characteristics at the Initiation of PD (T0) and at 10 Years (T1).

| | T0 | T1 | p value |
|---|---|---|---|
| Urine output (mL/day) | 1500 [1000–2000] | 0 [0–150] | **0.010** |
| Kt/V (mL/mn) | 1.56 +/–0.6 | 1.41 +/–0.479 | 0.800 |
| nPCR (g/kg/day) | 0.766 +/–0.21 | 0.615 +/–0.09 | 0.080 |
| WCC (mL/mn) | 92.4 +/–43.5 | 49 +/–21 | **0.010** |
| RKF (mL/mn) | 4.60 [1.44–7.70] | 0 [0–1.14] | **0.001** |
| Albumine (g/l) | 38.2 +/–6.08 | 37.1 +/–5.65 | 0.777 |
| LDL-Cholesterol (g/L) | 1.21 +/–0.410 | 1.04 +/–0.411 | 0.501 |
| Triglycerides (g/L) | 1.93 +/–1.03 | 1.69 +/–0.846 | 0.633 |
| Uric acid (mg/L) | 83.5 +/–18.5 | 63 +/–11.2 | **0.018** |
| Potassium (mmol/L) | 4.73 +/–0.66 | 4.34 +/–0.36 | 0.112 |
| Calcium (mg/L) | 79.7 +/–13 | 91 +/–8 | **0.033** |
| Bicarbonates (mmol/L) | 26.6 +/–2.07 | 17.9 +/–3.7 | **< 0.001** |
| Hemoglobin (g/dL) | 10.6 +/–2.07 | 11.1 +/- 1.65 | **0.0320** |
| Ultrafiltration (mL/day) | 400 [178–600] | 1000 [900–1500] | **< 0.001** |

hypocalcemic dialysate. These changes likely reflect a combination of treatments tailored to each patient, including oral calcium supplementation, vitamin D analogs, phosphate binders, and, when indicated, an active vitamin D analog (calcitriol/alfacalcidol) or a calcimimetic. Nine patients had hyperparathyroidism; three required parathyroidectomy, while the remaining six were managed conservatively with this individualized regimen to maintain calcium and phosphate within target ranges and minimize the risk of adynamic bone disease.

## MECHANICAL AND INFECTIOUS COMPLICATIONS

The median number of exit-site infections is 1 [0–2], while the peritonitis rate is 41 patient-months/peritonitis and 0.024 peritonitis/month-patient, corresponding to 41 patient-months per peritonitis. Five peritonitis episodes were relapse peritonitis, three of which were caused by *coagulase-negative Staphylococcus*, one by *Escherichia coli*, and one by *Streptococcus aureus* in individual patients (Table 3). Only three catheter changes were performed during this period.

Peritonitis episodes were managed according to the ISPD guidelines. Empiric therapy typically included cefazolin or vancomycin combined with ceftazidime ± an aminoglycoside, and treatment was subsequently adapted based on the causative organism and its antibiotic susceptibility. Catheter removal was reserved primarily for refractory peritonitis or cases where medical treatment failed. Although peritoneal permeability was not systematically reassessed after peritonitis, no clinical evidence of ultrafiltration failure or encapsulating peritoneal sclerosis was observed during follow-up.

Mechanical complications included catheter migration, catheter dysfunction, catheter perforation, and peritoneal leak, occurring in 4 (33.5%), 2 (18%), 3 (27%), and 1 (9%) patients, respectively. Some of these complications tended to occur early in the course of peritoneal dialysis, whereas others appeared later. However, no correlation was observed between the occurrence of these mechanical complications or peritonitis and the overall duration of peritoneal dialysis.

Although peritoneal permeability was not systematically reassessed after peritonitis, no clinical evidence of ultrafiltration failure or encapsulating peritoneal sclerosis was observed during follow-up.

## EVOLUTION AND MORTALITY

The average survival on peritoneal dialysis (PD) in this cohort was 10.4 ± 0.9 years. Seven patients are still undergoing PD. Three patients were transferred to chronic hemodialysis: one due to a *Candida albicans* peritonitis, and two due to a loss of ultrafiltration and poor dialysis clearance. One patient passed away due to septic shock. Only one patient received a kidney transplant, while three patients are on the national kidney transplant waiting list from a

**Tab. 3** Complications related to PD occurring in patients.

| Complications | | Patients (n = 12) |
|---|---|---|
| Mechanical | Catheter migration<br>Catheter dysfunction<br>Catheter perforation<br>Peritoneal leak | 4 (33.5%)<br>2 (18.0%)<br>3 (27.0%)<br>1 (9.0%) |
| Infectious | Exit site infection<br>Tunnel infection<br>Peritonitis<br>Repeat peritonitis<br>*Staphylocoque coagulase négative*<br>*Escherichia coli*<br>*Staphylocoque aureus*<br>Relapse peritonitis | 1 [0–2]<br>0<br>4 [2–4.25]<br>5<br>3<br>1<br>1<br>0 |

brain-dead donor. One patient refused the kidney transplant, and six patients are deemed non-transplantable due to specific comorbidities. No parameter was found to be associated with the survival of the technique beyond 10 years or with mortality.

## DISCUSSION

The survival of the peritoneal dialysis technique or the patient on PD reported in studies is often underestimated, since the final event for technique survival is the permanent transfer to hemodialysis, and the final event for patient survival is death. The recovery of kidney function and transfer to another center are censored events. For these reasons, the percentage of patients remaining on treatment is much lower than what is calculated based on current survival data of patients or the technique.

The survival rates on PD reported by different countries are highly variable and mainly depend on the incidence of kidney transplantation in each country. At the end of the 20th century and the beginning of the 21st century, the survival rate on PD for more than 8 years was 33% in Italy (2). Similarly, data from Australia and the United Kingdom show that only 0.4% and 1.4% of patients, respectively, remain on PD after eight years (3). In North America, the percentage of patients on PD for more than ten years ranges from 0.8% to 7.3% (4). Recently, a survival rate of 19.6% at 10 years was reported in Spain in 2013 (5), while Japanese data from 2018 reported a 15% survival rate of PD patients after eight years (6). It is important to note that Japan has a low transplantation rate (7). In the United States, the 10-year survival rate is 11%. Cardiovascular diseases remain the leading cause of death (8). Similarly, the long duration of peritoneal dialysis in our cohort can be explained by limited access to kidney transplantation and the presence of non-transplantable patients, as detailed in the results section. In our setting, the scarcity of available organs and medical contraindications to transplantation contribute to maintaining patients on long-term PD. Moreover, the good tolerance of PD, the low peritonitis rate, and adequate technique survival further supported the continuation of PD over many years.

Additionally, in 1996, De Vecchi et al. reported a prevalence of 7.8% of patients on continuous ambulatory peritoneal dialysis for more than 10 years, with a mean age of 50.8 years (9). In a second study, Abdel-Rahman et al. in 1997 reported that 7 patients with type 1 diabetes were among those who survived more than 100 months, with a mean age of 41.6 years. They represented 12% of the survivors and 16% of all type 1 diabetic patients, whereas none of the 24 type 2 diabetic patients survived more than 100 months (10). In 2024, Erol Demir et al. found a survival rate of 64.6% at 10 years and 41.1% at 15 years, with a mean age of 53 years. Diabetic nephropathy represented 6.4% of the causes of end-stage kidney disease (ESKD), and the factors associated with mortality were advanced age, male gender, and vascular access as the indication for PD (11).

In our study, tubulointerstitial nephropathy was the most common cause, and only one patient had diabetes. Our study showed that the 10-year survival rate was 5%. PD discontinuation in our study was mainly related to a loss of ultrafiltration due to peritoneal aging, and only one patient presented with *Candida peritonitis*, making the peritoneum unsuitable for exchanges.

Importantly, achieving long-term preservation of the peritoneal membrane depends on multiple strategies. In general, the literature recommends the use of biocompatible dialysis solutions, careful fluid management, strict prevention and prompt treatment of peritonitis, periodic assessment of peritoneal membrane function, and maintaining residual kidney function (12, 13). In our cohort, we observed that patient education, individualized dialysis prescriptions, early intervention for complications, and switching from CAPD to APD when indicated contributed significantly to long-term peritoneal membrane preservation. These measures likely played a key role in maintaining the technique beyond 10 years despite the advanced age of some patients and the natural decline in residual kidney function.

Finally, Xi Xia et al. (2020) demonstrated that long-term PD can be successfully performed, depending on the management of cardiovascular diseases and diabetes, as well as the preservation of peritoneal function. The 10-year survival rate in their study was 36%. In our study, the young age of our population (45.5 ± 16.5 years), low Charlson comorbidity index, and high educational level of patients contributed to the survival of the technique beyond 10 years (14).

Furthermore, complications related to prolonged use of PD, such as encapsulating peritoneal sclerosis (EPS), remain a major concern. EPS is rare but serious, reported in about 0.7% to 3.3% of long-term PD patients. None of our patients developed EPS (11).

Moreover, the preservation of residual kidney function plays a crucial role in the survival of the technique beyond 10 years. As shown in the study by Li et al. (2017), patients who maintain significant urine output after several years show much better clinical outcomes (15). However, in our study, the loss of residual kidney function in three patients was not a factor for PD discontinuation. In our patients, the decline in residual kidney function happened gradually, but it was most noticeable during the first 5 years of PD. After that, it slowed down and became more stable. At 10 years, only two patients still had a residual kidney function above 4 mL/min. This pattern is similar to what has been reported in previous reports, where the fastest drop in kidney function happens in the early years of PD, followed by a plateau.

Overall, maintaining technique survival is closely related to the prevention of peritoneal infection episodes, which remain a frequent cause of technique failure. A study by Mehrotra et al. (2016) showed that technique survival after 10 years strongly depends on reducing infectious episodes. The low peritonitis rate found in our study is associated with better survival on PD. The therapeutic education program, as well as retraining patients and staff, are important factors for improving survival (16).

Lastly, the small and highly selected group of patients who remained on PD beyond 10 years in our cohort illustrates the feasibility of long-term peritoneal dialysis even in challenging settings. Despite limited human resources,

with 1 to 2 dedicated PD nurses managing approximately 50 active patients per year, these patients successfully maintained the technique. All were well-educated and demonstrated excellent compliance, supported by a strong medical staff-patient relationship, which played a crucial role in achieving favorable outcomes. This insight highlights that with structured care, individualized management, and close monitoring, long-term PD can be safely and effectively sustained, providing valuable guidance for dialysis programs in similar resource-limited contexts.

## CONCLUSION

Although prolonged peritoneal dialysis beyond 10 years is uncommon, our experience shows that it is feasible with a combination of patient education, individualized care, and careful monitoring. Success depends on multiple factors: effective management of infectious complications, preservation of residual kidney function, use of biocompatible solutions, careful fluid management, optimized dwell times through CAPD to APD switching, and prompt treatment of peritonitis. Together, these strategies not only improve patient outcomes but also help preserve long-term peritoneal membrane function. Further research is needed to refine these approaches, extend peritoneal membrane health, and prevent complications such as encapsulating peritoneal sclerosis, particularly in patients who are not candidates for kidney transplantation.

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# Peripheral Microcirculation Alterations as an Indicator of Predisposition to Tendon Degeneration of the Shoulder Joint: A Preliminary Study

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ABSTRACT

Introduction: The etiology of rotator cuff tear (RCT) is multifactorial and includes extrinsic and intrinsic factors. Alterations of the peripheral microcirculation represent a main intrinsic etiological factor; recent evidence demonstrates that at the level of the rotator cuff tendons there is significant reduction in capillary density and microvascular blood flow. On the basis of the alterations of the microcirculation present at the level of the rotator cuff (RC) tendons, the aim of our study was to evaluate the possible presence of alterations of the peripheral nail microcirculation, through capillaroscopic examination, in a consecutive series of patients with RCT, comparing them with an adequate control group. The hypothesis of our study is that the alteration of the local microcirculation is accompanied in patients with RCT by an alteration of the peripheral microcirculation that may represent a systemic predisposing factor for tendon degeneration.

Materials and methods: A case-control study was conducted. The Case Group consisted of 82 patients (mean age 61 years ± 8) with RCT, the size of which was assessed intraoperatively and classified into small, large and massive according to Snyder; the control group was represented by 43 healthy subjects (mean age 63 years ± 9). All control subjects underwent ultrasound examination to objectively exclude rotator cuff tears. All participants underwent a nail capillaroscopic examination of the hands to evaluate morphological and dynamic parameters. The data was subsequently analyzed.

Results: In the Case Group, 34 patients had a small RC lesion, 23 had a large lesion, and 25 had a massive lesion. The main capillaroscopic differences between cases and controls were found in the morphology of the capillary loops and in the flow. In the group of cases, 50% have normal loops, 47.56% have tortuous loops and 2.44% have branched loops; in the control group 62.79% had normal loops, 34.88% had tortuous loops and 2.33% had branched loops. The capillary flow was normal in 46.34% of the cases group, granular in 48.78% and slowed in 2.44%. 95.35% of the control group had normal flow and 2.33% grainy flow. Regarding the severity of the lesion, no significant differences were found between patients with small, large and massive lesion (small lesion: 50% normal loops, 41.2% normal flow; large lesion: 52% normal loops, 47.8% normal flow; massive lesion: 48% normal loops, 48% normal flow).

Conclusions: The prevalence of capillaroscopic alterations was higher in patients with rotator cuff tears: the capillary loops are more tortuous and present ectasias more frequently than in the control group. Additionally, capillary flow in patients with RCT is grainier and slowed. However, the compromise of the capillary picture is not proportional to the severity of the tendon lesion, limiting the direct clinical applicability of this finding. The results support the hypothesis that peripheral microcirculation disorders constitute an etiological factor predisposing to tendon degeneration and, therefore, rupture. Further longitudinal studies are needed to assess whether these alterations can predict healing outcomes and risk of re-tear after surgical repair.

KEYWORDS

rotator cuff; peripheral microcirculation; tendon degeneration; capillaroscopy

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## INTRODUCTION

The rotator cuff (RC) is a muscle-tendon complex that provides stability and mobility to the glenohumeral joint. It consists of four muscles: supraspinatus, infraspinatus, teres minor, and subscapularis. Rotator cuff tears (RCT) are among the most common shoulder pathologies, with prevalence increasing significantly with age, reaching over 80% in individuals older than 80 years (19, 45).

The etiology of rotator cuff tears is multifactorial, involving both extrinsic factors (anatomical variants, mechanical impingement) and intrinsic factors (age, smoking, vascular alterations). Among intrinsic factors, alterations of the microcirculation play a crucial role, leading to cellular modifications that interfere with collagen turnover and predispose tendons to degeneration and rupture (9–12, 46, 47).

Recent studies using advanced imaging techniques have confirmed that reduced blood flow in specific tendon regions, associated with microcirculatory disorders, contributes significantly to tendon degeneration. Biberthaler et al. (13) demonstrated through arthroscopic orthogonal polarization spectral imaging a marked reduction in functional capillary density at the edges of degenerative rotator cuff lesions compared to control tissue. More recent investigations have shown that microvascular blood flow is not uniform throughout the supraspinatus tendon and is significantly lower in pathologic tendons compared to normal tendons (46, 48).

Tendon degeneration is characterized by thinning of collagen fibers, loss of structural organization, decreased fibroblast number, and progressive reduction in blood vessel density. These changes result in poor healing capacity and high risk of recurrence after surgical repair (3, 48, 50).

Since microcirculatory alterations are recognized as an important etiological factor in tendon injury, we investigated whether patients with rotator cuff tears present evident peripheral capillary alterations detectable through nailfold capillaroscopy. Capillaroscopy is a non-invasive, safe, and well-established method for assessing structural and functional alterations of the microcirculation (15, 51, 52). This technique has gained increasing recognition beyond its traditional use in connective tissue diseases, with recent applications in various conditions affecting peripheral microcirculation, including metabolic and cardiovascular disorders (53, 54).

The aim of our preliminary study is to evaluate the presence of peripheral capillary alterations (structural and flow-related) in a group of patients with rotator cuff tears compared to a control group of healthy subjects, and to assess whether there is a correlation between the severity of the tendon lesion and the degree of capillary alteration.

## CLASSIFICATION OF ROTATOR CUFF TEARS

Rotator cuff tears can be classified based on location (articular, bursal, intratendinous), tendon involved, and lesion size. For this study, we used Snyder's classification (36), which distinguishes:

Partial tears:
- Grade 0: normal cuff with bursitis/synovitis
- Grade 1: modest inflammation without tendon lesions
- Grade 2: modest tendon degeneration without flap
- Grade 3: degeneration and fragmentation with good tissue quality
- Grade 4: partial lesion with severe degeneration

Complete tears (used in our study):
- Type I: small, complete, punctate lesion
- Type II: small lesion (<2cm) involving single tendon without retraction
- Type III: large lesion (3–4cm) involving single tendon with retraction
- Type IV: massive lesion involving two or more tendons with retraction and fibrosis

## CAPILLAROSCOPY

Capillaroscopy allows microscopic visualization of the nailbed capillary pattern (15). The technique is particularly valuable for diseases involving microcirculatory dysfunction, offering advantages including non-invasiveness, high sensitivity, ease of execution, and potential predictive value (16–18, 51).

Key capillaroscopic parameters evaluated include:
Morphological (static) parameters:
- Loop morphology (hairpin, tortuous, branched, arborescent)
- Capillary density (normal: 9–14 capillaries/mm)
- Presence of avascular areas
- Ectasias and megacapillaries
- Microhemorrhages and hemosiderin deposits

Functional (dynamic) parameters:
- Flow characteristics (continuous, granular, slowed, intermittent)

Recent advances in quantitative capillaroscopy, including automated image analysis, have improved the objectivity and reproducibility of this technique (55, 56).

## MATERIALS AND METHODS

A retrospective case-control study was conducted on 125 subjects. Group 1 (cases) comprised 82 patients (mean age 61 years ± 8) with rotator cuff tears repaired arthroscopically, while Group 2 (controls) consisted of 43 healthy subjects (mean age 63 years ± 9).

In the case group, diagnosis of rotator cuff tear was performed through physical examination and confirmed with Magnetic Resonance Imaging (MRI). The lesion size was assessed intraoperatively and classified according to Snyder's method as small, large, or massive.

Exclusion criteria for both groups:
- Scleroderma, systemic lupus erythematosus, Raynaud's phenomenon, and other rheumatic pathologies (which present characteristic capillaroscopic alterations)

- Permanent nail polish
- History of trauma due to domestic or professional/manual activity
- Diabetes mellitus, uncontrolled hypertension, or other systemic conditions known to significantly affect microcirculation

For the control group:
- Physical examination of anterior and posterosuperior rotator cuff tendons was performed
- All control subjects underwent shoulder ultrasound examination to objectively exclude rotator cuff tears, addressing the known presence of asymptomatic tears in the general population
- Subjects positive on clinical tests (internal rotation lag sign, Jobe test, external rotation lag sign) or showing tears on ultrasound were excluded

Inclusion Criteria (Cases)
- Diagnosis of rotator cuff tear
- RCT repaired arthroscopicallyand classified

Exclusion Criteria (Cases)
- Rheumatic pathology
- History of trauma
- Permanent nail polish
- Uncontrolled metabolic/vascular conditions

Inclusion Criteria (Controls)
- No rotator cuff tear
- Negative ultrasound for RCT

Exclusion Criteria (Controls)
- Rheumatic pathology
- History of trauma
- Positive physical examination
- Positive ultrasound findings
- Permanent nail polish

## CAPILLAROSCOPIC EXAMINATION PROTOCOL

After 15 minutes of acclimatization in a room at 20–22 °C, participants sat with hands placed at heart level. Excluding thumbs, a drop of clearing oil (cedar or paraffin) was applied to nailbeds of fingers 2–5 on both hands to reduce light reflection and improve visualization.

A video-capillaroscope with optical probe was used for direct contact with the nailbed. The probe emits cold incident light, providing three-dimensional images without causing reactive hyperemia. Examination was performed first with low magnification (20×) for global assessment of the nailbed and microvascular network, then with high magnification (200×) for detailed capillary flow evaluation. Images were viewed on a high-definition color monitor and stored digitally.

The following capillaroscopic parameters were evaluated:

- Loop morphology (normal, tortuous, branched, arborescent)
- Capillary density (normal, reduced, very reduced)
- Avascular areas
- Subpapillary venous plexus visibility
- Megacapillaries presence
- Ectasias and/or microaneurysms
- Neoangiogenesis (absent, limited, diffuse)
- Hemosiderin deposits (absent, rare, frequent)
- Background color (rosy, deep red, cyanotic, pale)
- Pericapillary edema (absent, mild, intense)
- Capillary flow

The characteristic capillaroscopic pattern for each patient was determined by identifying parameters present in at least 5 out of 8 examined fingers as dominant.

## RESULTS

### OVERALL COMPARISON: CASES VS CONTROLS

Loop Morphology:
- Cases: 41 patients (50%) normal loops, 39 (47.56%) tortuous loops, 2 (2.44%) branched loops
- Controls: 27 subjects (62.79%) normal loops, 15 (34.88%) tortuous loops, 1 (2.33%) branched loops
- No arborescent loops in either group

Capillary Density:
- Cases: 81 (98.78%) normal density (~10 capillaries/mm), 1 (1.22%) reduced density
- Controls: 100% normal density

Avascular Areas:
- Cases: 0%
- Controls: 0%

Subpapillary Venous Plexus (PVSP) Visibility:
- Cases: 71 (86.59%) barely visible, 11 (13.41%) visible in some periungual areas
- Controls: 30 (69.77%) barely visible, 13 (30.23%) visible in some periungual areas

Megacapillaries:
- Cases: 0%
- Controls: 0%

Ectasias and Microaneurysms:
- Cases: 19.51% present
- Controls: 0%

Neoangiogenesis:
- Cases: 2/82 patients showed limited neoangiogenesis
- Controls: 0%

Hemosiderin Deposits:
- Cases: 5/82 patients
- Controls: 0%

Background Color:
- Cases: 76/82 pink, 6/82 other colors
- Controls: 39/43 pink, 4/43 other colors

Pericapillary Edema:
- Cases: 45.12% absent, 54.88% present (32.93% mild, 19.51% moderate, 2.44% intense)
- Controls: 58.14% absent, 41.86% present (34.88% mild, 6.98% moderate)

Capillary Flow (Most Significant Finding):
- Cases: 38 (46.34%) normal flow, 40 (48.78%) granular flow, 2 (2.44%) slowed flow, 2 not assessable
- Controls: 41 (95.35%) normal flow, 1 (2.33%) granular flow, 1 (2.33%) slowed flow

### SUBGROUP ANALYSIS BY LESION SIZE

Small Lesions (n = 34):
- Morphology: 50% normal loops, 44.12% tortuous loops, 5.88% branched loops
- Flow: 41.2% normal, 55.88% granular (1 not assessable)

Large Lesions (n = 23):
- Morphology: 52.17% normal loops, 47.83% tortuous loops
- Flow: 47.83% normal, 43.48% granular, 4.35% slowed

Massive Lesions (n = 25):
- Morphology: 48% normal loops, 52% tortuous loops
- Flow: 48% normal, 44% granular, 4% slowed (1 not assessable)

No significant differences were found between small, large, and massive lesion groups in terms of capillaroscopic alterations.

## DISCUSSION

Our study evaluated the peripheral capillary pattern in patients with rotator cuff tears compared to healthy controls. The definition of a "normal" capillaroscopic picture remains subject to discussion, as various studies demonstrate significant variability in the healthy population.

Previous studies have documented this variability. Andrade et al. (39) demonstrated in 800 healthy subjects that capillary morphological anomalies were more frequent in subjects over 40 years (42% vs 33%). Fahrling et al. (40) found tortuous loops in 64% of healthy individuals. Hoerth et al. (41) developed a scoring system recognizing that capillary changes occur frequently among healthy individuals, finding that only 15% of 120 healthy volunteers showed no deviations in morphology, hemorrhages, or capillary density.

Recent advances in capillaroscopy have improved our understanding of normal variants. Ingegnoli et al. (42–44) described three main "normal" patterns: the "normal" pattern with 2–5 U-shaped capillaries/mm and ≤2 tortuous loops/mm; the "perfect normal" pattern with ≥5 U-shaped capillaries/mm; and "unusual normality" with at least 1 tortuous/arborescent loop or microhemorrhage. More recent work has emphasized the importance of standardized evaluation methods and quantitative assessment to reduce subjectivity (55, 56).

Our study demonstrated that the capillaroscopic picture of patients with rotator cuff tears is more compromised, both morphologically and dynamically, compared to controls. Morphologically, 50% of patients with RCT present alterations in capillary loop morphology, predominantly tortuous loops. Dynamically, over half of patients with RCT present altered capillary flow, represented in almost all cases by granular flow.

These findings are consistent with recent literature demonstrating the role of microcirculatory dysfunction in rotator cuff pathology. Gumina et al. (49) recently demonstrated through arthroscopic evaluation that macroscopic vasculature of the rotator cuff is influenced by pre-existing diseases and lifestyle factors that impair peripheral microcirculation.

However, a critical finding of our study is that considering only the case group, we did not demonstrate more severe peripheral microcirculation impairment in patients with greater tendon rupture severity. In patients with small, large, or massive lesions, approximately half presented morphological alterations of capillary loops and altered capillary flow, with no significant differences between groups.

This lack of correlation between peripheral microcirculatory alterations and tear size limits the direct clinical applicability of capillaroscopy for surgical planning or predicting tear progression. While capillaroscopy may identify patients with systemic microcirculatory dysfunction predisposing to tendon degeneration, it cannot stratify them based on current tear severity.

## CLINICAL IMPLICATIONS AND LIMITATIONS

Our study has several important limitations that must be acknowledged:
1. Sample size: The relatively small number of subjects, particularly in the control group (n = 43), may limit the generalizability of findings.
2. Cross-sectional design: This study cannot assess whether capillaroscopic alterations predict healing outcomes or risk of re-tear after surgical repair, which would be the most clinically relevant application.
3. Definition of normal capillaroscopy: Despite recent advances (55, 56), significant variability in "normal" capillaroscopic patterns remains a challenge for interpretation.
4. Control group validation: Although we added ultrasound examination to objectively exclude rotator cuff tears in controls, this approach may not detect all small or partial tears that could be identified with MRI.
5. Lack of correlation with tear size: The absence of correlation between peripheral capillaroscopic findings and lesion severity significantly limits the practical utility of this examination for surgical decision -making.

Despite these limitations, our findings support the hypothesis that peripheral microcirculation disorders represent a systemic predisposing factor for tendon degeneration. Capillaroscopy, considering its ease of execution and low cost, could potentially be used to identify patients at higher risk for tendon pathology or poor healing. However, prospective longitudinal studies are needed to:
1. Assess whether capillaroscopic alterations predict healing outcomes after rotator cuff repair.
2. Evaluate the risk of re-tear in relation to peripheral microcirculatory status.
3. Determine if interventions targeting microcirculatory function could improve surgical outcomes.

Recent evidence suggests that biological augmentation strategies aimed at improving vascularization during healing may enhance outcomes (57). Understanding which patients have underlying microcirculatory dysfunction could help identify those who would benefit most from such interventions.

## CONCLUSIONS

The prevalence of capillaroscopic alterations was higher in patients with rotator cuff tears: 47.56% of patients with RCT had tortuous capillary loops compared to 34.88% of controls. Most significantly, granular capillary flow was found in 48.78% of cases compared to only 2.33% of controls, while normal flow was present in 95.35% of controls versus 46.34% of cases.

However, the impairment of the capillary picture, assessed through capillaroscopy, is not proportional to the severity of the tendon rupture when comparing small, large, and massive tears. This lack of correlation limits the direct clinical applicability of capillaroscopy for surgical planning or predicting tear progression.

This preliminary study highlights that alteration of peripheral microcirculation is a frequent finding in patients with rotator cuff tears. The results support the hypothesis that peripheral microcirculation disorders constitute a systemic etiological factor predisposing to tendon degeneration and rupture.

Future directions should include:

1. Prospective longitudinal studies to assess whether capillaroscopic alterations predict healing outcomes and re-tear risk after surgical repair.
2. Investigation of whether interventions targeting microcirculatory function could improve surgical outcomes.
3. Larger multicenter studies with standardized quantitative capillaroscopy protocols to better define clinically relevant thresholds.

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