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CKJ Review

The Forgotten Sex
gender disparities in kidney disease

CKJ REVIEW

Why do we keep ignoring sex in kidney disease?

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ABSTRACT

Throughout the history of nephrology, little attention has been paid to the sex and gender differences in kidney disease. This lack of awareness prevents optimal diagnosis and management of kidney disease. In today's world of precision medicine, it is imperative to appreciate the differential factors regarding gender and kidney disease.
This editorial summarizes the up-to-date literature regarding sex and gender differences in kidney disease and considers areas where knowledge is incomplete and where further research is needed. We address sex-specific effects on chronic kidney disease epidemiology; risks of dialysis underdosing and medication overdosing in women; unexplained loss of female sex advantage in life expectancy during dialysis, and impact of sex on diagnosis and management of genetic kidney disease. We also aim to highlight the impact of gender on kidney health and raise awareness of disparities that may be faced by women, and transgender and gender-diverse persons when a male-model approach is used by healthcare systems. By understanding the link between sex and kidney disease, kidney specialists can improve the care and outcomes of their patients. In addition, research on this topic can inform the development of targeted prevention and intervention strategies that address the specific needs and risk factors of different populations.

LAY SUMMARY

Until recently, the differences attributed to sex and gender have not been of interest for kidney specialists. That was an obvious omission which might result in inappropriate diagnosis and treatment. Today, as the individual approach becomes the core of medicine, factors regarding gender and kidney disease should be better acknowledged.
This editorial summarizes the up-to-date literature regarding sex and gender differences in kidney disease. In addition, it shows what is not known yet and in which direction future research should be planned. Here we discuss the specific problems in diagnosis and treatment of kidney diseases. We also aim to highlight the impact of gender on kidney health and raise awareness of disparities that may be faced by women, and transgender and gender-diverse persons when a male-model approach is used by healthcare systems. Finally, we propose some solutions that may be pursued to improve clinical practice in the nearest future.

Keywords: dialysis, disparity, gender, pharmacokinetics, women

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INTRODUCTION

Although women and men share nearly identical genetic information, their phenotypes are distinct. Women may react differently to treatment, may manifest disease symptoms in a different way and may have profoundly different needs from a social or cultural perspective. In 1991, McMurray *et al*. claimed gender disparities in clinical decision-making and pointed to the fact that medical treatments for women are based on the male model, regardless of biological differences between sexes [1].

In the modern era, biological (sex) and sociocultural (gender) conditioning are readily separated although both may fundamentally modulate healthcare needs and outcomes. The term sex is the one most established in terms of pre-clinical and clinical research. Sex influences choice, efficacy and outcome of therapy in many clinical areas (Table 1). This is a consequence of sex-specific effects of genetic polymorphisms, different function of ion channels in heart or kidney, variation in body composition, and sex hormones' influence on pharmacokinetics and pharmacodynamics [2].

Understanding those processes and utilizing the knowledge of sex differences warrants enhanced therapeutic effectiveness and minimizes drug side effects (Table 2). Based on this knowledge one may expect that women need higher initial doses of calcineurin inhibitors per kilogram of body weight, have lower probability of developing severe infection after biological therapy and experience greater suppressive effects of cortisol. Nevertheless, the relevance and consequences of these hypotheses are largely unknown.

Table 1: Examples of known therapeutical areas influenced by sex.

Therapeutic area	Examples of differences	References
Cardiovascular disease	Influence of sex hormones on regulation β-adrenergic receptors in cardiovascular system Increased hypotensive action of β-blockers in women Higher incidence of cough after ACEi in women	[49, 50, 51]
Anticoagulation and antithrombotic treatment	The bioavailability of acetylsalicylic acid is greater but platelet inhibition is lower in women	[52, 53]
Antiarrhythmic	Influence of sex hormones on the length of QT Increased risk of Torsade de Pointes in women Higher risk of tachycardia in women	[54, 55]
Pain and anesthesia	Women tend to experience more severely chronic pain	[56, 57]
Depressive disorders	Sex hormones influence the pharmacokinetic of antidepressants More adverse events after TCA in women	[58]
Oncologic diseases	Checkpoint inhibitors are less beneficial in women	[59]
COPD	Better response to anticholinergic bronchodilators due to greater expression of M2 over M3 muscarinic receptors in women	[60]
Anti-inflammatory therapy	Higher risk of serious infection during biological treatment in men	[61]
Anti-viral therapy	Humoral immune response after vaccination higher in women More adverse effects and toxicity of anti-viral drugs in women	[62, 63]
Thyroid disorders	Thyroxine requirements are higher in men	[64]

COPD: chronic obstructive pulmonary disease; TCA: tricyclic antidepressant.

Table 2: Mechanisms underlying sex differences in pharmacokinetics and pharmacodynamics of drugs—adapted from [2].

Pharmacokinetics	Absorption	Gastric enzymes
		Gut motility
		Microbiota
		Transporting proteins
	Distribution	Body composition
		Cardiac output
		Organ blood flow
	Liver metabolism	CYP3A4, CYP2D6, CYP2C19, CYP1A2
	Elimination	Kidney clearance
		Liver function
		Pulmonary expiration
		Plasma proteins concentration
Pharmacodynamics	Sex-specific conditions	Contraception
		Pregnancy
		Menopause

CYP3A4, CYP2D6, CYP2C19, CYP1A2: cytochrome P 450 isoenzymes named according to their coding chromosomes (activity in women CYP3A4 ↓, CYP2D6↑, CYP2C19↑, CYP1A2↑).

AWARENESS OF SEX DIFFERENCES IN NEPHROLOGY

Sex differences have not been extensively explored in nephrology. In 2018, World Kidney Day coincided with International Women's Day and led to increased awareness of women's health by publishing a document entitled 'Women and Kidney Diseases: Questions Unanswered and Answers Unquestioned' [3]. That initiative paved the road towards incorporating sex disparities in nephrology into the research agenda at both basic and clinical levels. Nevertheless, kidney disease is misidentified as not being influenced by sex or gender by 44.1% of 1323 European internists who were surveyed by the Internal Medicine Assessment of Gender differences in Europe (IMAGINE) working group [4].

In February 2023 the first KDIGO Controversies Conference on Women and Kidney Health took place in Athens. A multidisciplinary team involving nephrologists, obstetricians, specialists in reproductive health and patients, amongst others, came together with the primary aim of identifying gender and sex issues in kidney care. There was a strong focus on improving the reproductive care of women with established chronic kidney disease (CKD) and women who develop hypertensive disorders of pregnancy or pregnancy-related acute kidney injury (AKI). Ultimately, this KDIGO meeting sought to describe current best practice, to identify areas of uncertainty and controversial issues, and to outline essential areas of research required to improve the management of women with CKD [5].

How do men and women differ? Sex associated differences of the kidney

Sex differences in kidney structure and function are known across species. Kidney mass, including volume of cortex, is greater in males in humans and rodents [6], while the size of medulla and length of thick ascending limbs prevails in female rats [7]. Interestingly, the latter dimorphism does not translate into better concentration capacity, which is greater in males [7]. This could be explained by the higher (up to 80%) expression of aquaporin 1 in male kidneys. Sex differences have also been described in other transporters. For example, expression of sodium-glucose cotransporter 2 is higher in kidneys of female rats [6].

Haemodynamics

Kidney haemodynamics may also differ across sexes, with higher glomerular vascular resistance reported in female rodents which presumably explains greater urinary protein excretion in males [8, 9]. Other functional differences include the role of nitric oxide (NO), which is higher in pre-menopausal women than in men, related to increased expression of endothelial NO synthase activity [10]. NO contributes to kidney hemodynamics, regulating the medullary blood flow, pressure natriuresis, tubulo-glomerular feedback and sympathetic system activity [11, 12].

Sex hormones

Furthermore, sex steroid hormones are believed to play a critical role in aggravation or inhibition of kidney damage [13]. In experimental models of polycystic kidney disease (PKD) or ischaemic–reperfusion kidney injury, oestrogens delayed processes of apoptosis and fibrosis [14]. In humans, the course of immunoglobulin A nephropathy, membranous nephropathy or PKD is more aggressive in men [14]. In general, testosterone is believed to increase oxidative stress and activate renin–angiotensin system (RAS) while oestrogens exhibit renoprotective effects [13, 14]. Counterintuitively, the use of oestrogen–progesterone oral contraception seems to be a risk factor for CKD progression, pointing to the fact that there are many gaps in our understanding of those processes and their clinical importance is largely unknown.

Chronic kidney disease

The recent analysis the SCREAM (Stockholm Creatinine Measurement from outpatient care project) cohort ($n = 227\,847$; 45% men) revealed sex differences in detection, recognition, monitoring and treatment of CKD [15]. They discriminated against women, persisted over time and were difficult to explain [15]. To some extent, this knowledge is not new. The paradox of women experiencing a higher prevalence of CKD, yet being less likely to be treated with dialysis or kidney transplantation has been found repeatedly and in diverse geographical locations [16, 17]. For many years, researchers were puzzled by this finding and hypothesized that formulas estimating glomerular filtration rate (eGFR) may overestimate CKD in women, or that kidney disease may progress more slowly in women [18]. Recently, the latter theory has been confirmed in a study that measured GFR decline with the use of iohexol clearance (Renal Iohexol Clearance Survey, Norway) and found it to be 25% steeper in men [19]. As the rate of kidney function decline does not fully explain the observed sex differences in epidemiology, cultural and social factors have been highlighted as possible contributors. This suggests that the differences may in part be explained by men having better education, higher income, better access to healthcare facilities and improved health literacy. However, this seems improbable given that the observed differences are reproducible across all geographical regions and are stable over decades of profound social change [20]. Interestingly, CKD is repeatedly reported among the 10 leading causes of death for women but not for men [21]. Thus, it is conceivable that biological sex does indeed contribute to the pathogenesis of kidney disease.

THE EXTENT OF THE PROBLEM

In the era of precision and personalized medicine, the obvious biological difference between sexes should not be ignored. The known differences regarding sex and kidney disease are summarized in Table 3.

Standard of care

Stratification by sex revealed that CKD care was more likely to conform to recommendations for men than for women in testing, monitoring of kidney function and use of recommended medications [22]. RAS inhibitors (RASi) are less frequently prescribed to eligible women [odds ratio (OR) 0.89, 95% confidence interval (CI) 0.83–0.94] [22, 23]. The rationale for the underutilization of angiotensin converting enzyme inhibitors/angiotensin-receptor blocker (ACEi/ARB) could in part be ascribed to less frequent urinary/creatinine albumin ratio testing (OR 0.93, 95% CI 0.91–0.96) [22], but could also be explained by the fact that these medications are contraindicated in women of childbearing potential without reliable contraception [24, 25]. Alternatively, some women may not get prescribed these medicines at all due to indecisiveness as regards future pregnancy, or may

Table 3: Established facts about sex and gender differences in kidney diseases.

Characteristic in women	Supporting evidence
Higher prevalence of CKD	Carrero *et al.*, *Nat Rev Nephrol* 2018 [17] Melsom *et al.*, *J Am Soc Nephrol* 2022 [19] Bikbov *et al.*, *Nephron* 2018 [16]
Autoimmune diseases targeting kidneys are more prevalent	Piccoli *et al.*, *Kidney Int Rep* 2018 [3]
Lower probability of testing for albuminuria	Bello *et al.*, *JAMA Netw Open* 2019 [22]
Less common initiation of ACEi/ARB	Qiao *et al.*, *Hypertension* 2020 [23]
Pregnancy associated complications including CKD	Zhang *et al.*, *Clin J Am Soc Nephrol* 2015 [65]
GFR decline is slower	Melsom *et al.*, *J Am Soc Nephrol* 2022 [19]
Lower eGFR at referral	John *et al.*, *Am J Kidney Dis* 2004 [66]
Lower number of women starting KRT	Carrero *et al.*, *Nat Rev Nephrol* 2018 [17]
Higher mortality on dialysis	De La Mata *et al.*, *BMJ* 2021 [29] Chen *et al.*, *Perit Dial Int* 2021 [67] Carrero *et al.*, *Clin J Am Soc Nephrol* 2011 [31]
Lower probability to have an arteriovenous fistula as a vascular access	Shah *et al.*, *Am J Nephrol* 2018 [68] Markell *et al.*, *Hemodial Int* 2018 [35]
Higher risk of peritonitis on PD	Kotsanas *et al.*, *Nephrology (Carlton)* 2007 [69]
Higher risk of encapsulating peritoneal sclerosis	Guest *et al.*, *Perit Dial Int* 2009 [70]
Higher ESA demands on dialysis	Ryta *et al.*, *Int Urol Nephrol* 2017 [33]
Higher incidence of depression and restless leg syndrome	Guglielmi, *Adv Chronic Kidney Dis* 2013 [71] Gitto *et al.*, *Int J Health Policy Manag* 2015 [72] Merlino *et al.*, *Neurol Sci* 2012 [73]
Lower dialysis adequacy	Lowrie *et al.*, *Kidney Int* 2004 [74] Depner *et al.*, *Kidney Int* 2004 [75]
Lower probability to receive kidney transplant	Wolfe *et al.*, *Am J Kidney Dis* 2000 [76]
Higher probability to become a living kidney donor	Gill *et al.*, *J Am Soc Nephrol* 2018 [77]

PD: peritoneal dialysis.

experience a higher burden of side effects. Additionally, even higher disproportion exists in non-prescribing statins between sexes (OR 0.90, 95% CI 0.87–0.93 for eligible men vs women) [23].

The use of combined oestrogen–progesterone oral contraceptive pills can be associated with a significant increase in blood pressure and albuminuria as well as kidney function decline [26–28], and for that reason it seems that women of childbearing age may be trapped in a vicious circle. For many of them, non-initiation of RASi is the comfortable or 'easiest' option. This ambiguity applies also to initiation hesitancy and premature cessation of other crucial medications, for example mycophenolate mofetil and tolvaptan. For the latter, a demand for reliable contraception can confuse certain patients who may have previously been told to avoid oestrogens due to the risk of triggering lupus flare or progression of liver cystic disease.

Mortality

Although the life expectancy of women in the general population exceeds that of men, this does not hold true in kidney replacement therapy (KRT) patients. Data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) show that standardized mortality rate compared with the general population is higher in women on dialysis than in men [29]. Women have 11% (95% CI 11.2–11.5) higher excess mortality at any given time, and on average had four more years of life lost than their male counterparts [29]. The excess mortality in women were amplified in those who were younger [29]. The detailed analysis of the same dataset revealed a higher risk of all-cause mortality was driven by higher mortality from infections and dialysis withdrawals [30].

The loss of the survival advantage of women on dialysis was observed also in comparison of mortality rate in the European incident dialysis patients from European Renal Association Registry with the European general population (Eurostat) [31]. Again, the difference was attributed to increased non-cardiovascular mortality in women [31].

Finally, the mortality risk was higher in women versus men among kidney graft recipients of all ages in three large transplant databases [32].

Disparity in kidney replacement therapy

There is a risk of overestimating dialysis adequacy in women. Men have greater total body water volume (V) than women with the same body surface area. This occurs because woman have proportionally greater total body fat mass, thus for a given weight, the male V is larger than the female V. However, there is no provision for adjusting Kt/V targets accordingly.

Furthermore, the same haemoglobin targets are used in both sexes, risking overexposure of erythropoietin-stimulating agent (ESA) in women [33]. Indeed, the prescription of ESA per kg body weight has been reported to be significantly higher in women than men.

Women with CKD have a 2-fold increase in bone fractures, which does not translate into sex-specific vigilance in guidelines on CKD–metabolic bone disease or osteoporosis [34].

Any of these examples may be enough to explain why mortality rates on dialysis are higher in women than men. Unfortunately, there are many other explanations, including less frequent use of arterio-venous fistulas (AVF) (OR 0.69, 95% CI 0.67–0.71) [35], higher incidence of depression and overall very poor quality of life (Table 3). Women are arbitrarily disqualified from AVF procedures due to misconception that vessel diameter is smaller, overlooking that outcomes are equally successful for both sexes [36].

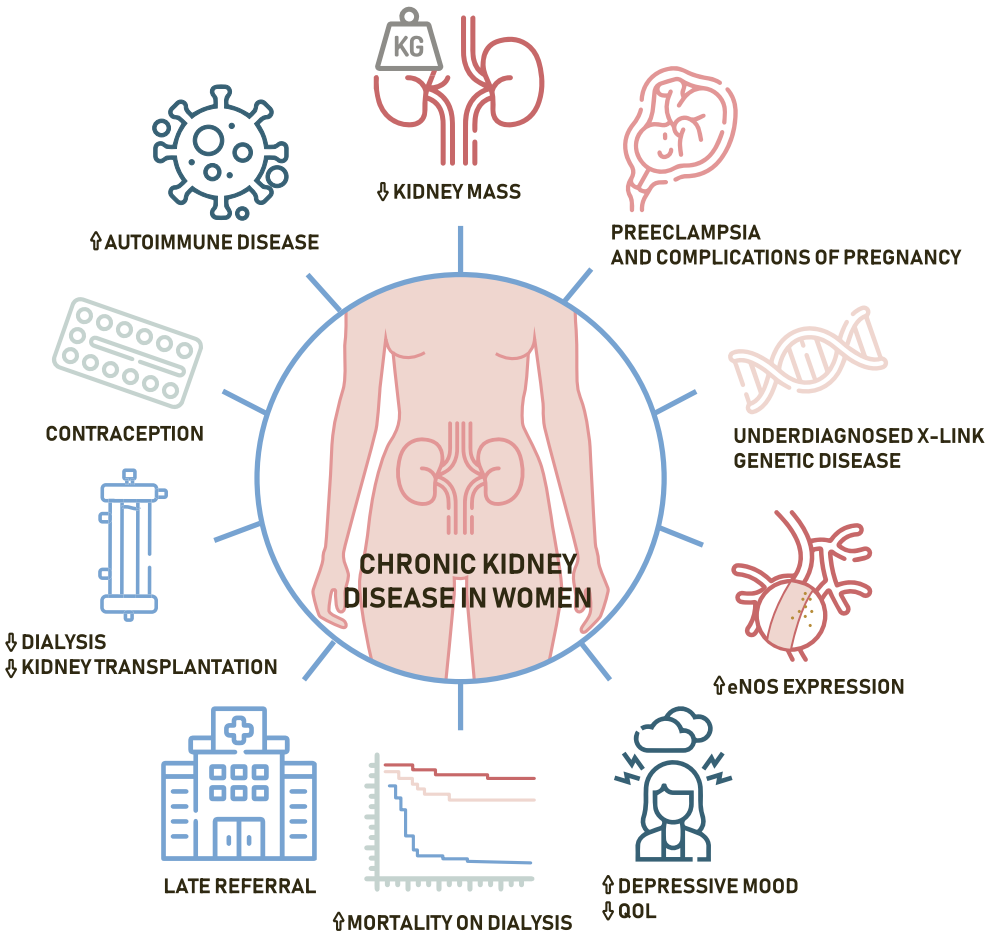

Figure 1: Chronic kidney disease in women.

Possibly due to cultural and social conditioning, women choose conservative treatment of CKD much more frequently than their male counterparts and are less likely to receive a kidney transplant. On the other hand, women are more likely to donate a kidney, even although the outcomes of transplantation of sex-mismatched kidneys seems less optimal [37, 38]. The mortality risk seems to be higher in women receiving a kidney transplant from men [32].

Inherited kidney diseases

Some ambivalence exists when considering inherited kidney diseases. For many years, women with Alport syndrome or Fabry disease were carelessly referred to as 'carriers'. It has only recently been acknowledged that a significant percentage of these 'carriers' may eventually need KRT and deserve careful medical surveillance [39, 40]. Additionally, women with X-linked kidney diseases are also underdiagnosed. The algorithms used to diagnose rare conditions based on clinical traits rely on male symptoms which are more severe and of earlier onset. Therefore these tools perform very poorly for making a diagnosis in women with X-linked diseases [41].

Complications of pregnancy

Pregnancy is the most prevalent cause of AKI in women of childbearing age and remains the leading cause of maternal morbidity and mortality [42]. There is a wide variety of pregnancy-specific causes of AKI that comprises, among others:

- hyperemesis gravidarum
- preeclampsia, HELLP (haemolysis, elevated liver enzymes and low platelets syndrome), TTP (thrombotic thrombocytopenic purpura) and hemolytic uremic syndrome
- septic abortion
- placenta abruption

Pregnancy-related AKI is associated with adverse fetal outcomes, increased mortality and prolonged hospital stay, but also with higher risk of cardiovascular events [43]. AKI preceding pregnancy increases the risk of preeclampsia and pre-term birth [42], while pregnancy-associated AKI and hypertensive disorders of pregnancy are risk factors for CKD [44, 45]. The latter finding should warrant CKD screening in women with pregnancy complications in medical history.

Gender matters

Focusing on biological aspects of sex divergence should not overshadow the gender construct, which plays a role in maintaining social, economic and cultural barriers. This is reflected in suboptimal health of transgender and gender diverse individuals [46]. In a recent analysis of University of Alabama database, the prevalence of CKD and AKI in a transgender cohort was as

high as 36% and 32% [47]. This could be attributed to side effects of treatment with gender-affirming hormonal therapy but likely also to stress, discriminatory policies and unmet healthcare needs, particularly secondary to the lack of awareness amongst medical professionals.

There are a few specific aspects that nephrologists should be aware of:

- the prevalence of AKI and CKD in transgender population is higher than in their cisgender counterparts [47]
- eGFR measures may be subject to bias due to changed muscle mass after initiation of hormone therapy which could be critical in qualification for kidney donation
- testosterone administration may have deleterious kidney effects
- there is an increased thromboembolic risk of oestrogen therapy
- spironolactone is often used as adjunctive anti-androgenic therapy and carries a risk of several side effects [48]

WHICH QUESTIONS ARE UNANSWERED AND WHAT SOLUTIONS COULD BE PROPOSED?

Mechanisms and medical consequences of differences between men and women receive increased attention among nephrologists. There are several potentially important sex-associated risk factors for CKD that are not modifiable (kidney mass, sex hormones and NO production) but there are modifiable risk factors too, including complications of pregnancy and poor health-related quality of life (HRQOL).

Regardless, crucial questions remain unanswered:

- Are there any sex differences in responses to kidney therapeutic measures?
- Should we make dose adjustments according to sex?
- Should we provide gender oriented psychological support?
- How can we use collected knowledge in guidelines?
- What can we do to avoid discrimination and prevent disparities?

Despite the complexity of the issue, we should be much more proactive in identifying solutions for the benefit of patients:

- nephrologists could gain from including some of the presented points into training curricula
- unraveling the role of physiological differences between sexes should receive higher priority in basic science studies
- sex-based equity in planned clinical trials may be achieved, by promoting recruitment of women, avoiding women-specific exclusion criteria and addressing barriers that affect women
- editorial boards of scientific journals may require sex-stratified analysis before considering accepting articles for publication
- every effort should be made to analyse existing evidence for differences in outcomes between men and women
- task force of could be set-up for generating best practice guidelines

CONCLUSIONS

Sex differences in nephrology are vastly underexplored. Our main focus was to highlight this issue. As researchers and clinicians, we need to be aware of the potential bias and should be able to offer our patients the best healthcare to meet their individual needs. That must include personalization of therapies by taking account of sex and gender. Promoting the representation of women in clinical trials, increasing awareness of sex and gender disparities, improving pregnancy care, and performing sex-stratified analyses of existing and future studies might be effective tools in attaining this goal. It is plausible that exploring hypotheses and seeking answers could be time consuming and difficult to achieve in this complex field blurred by many confounders. This does not mean that we should not start.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

M.J.S. is Editor Emeritus of *CKJ* and reports honorarium for conferences, consulting fees and advisory boards from AstraZeneca, NovoNordsik, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, ICU Medical, Fresenius, Travere therapeutics and Boehringer. M.J. reports a grant (2018/30/M/NZ5/00 480) from the National Science Centre, Poland and honorarium for lectures from Chiesi, Fresenius Kabi and Swixx. R.T.'s research is funded by Fundació la Marató de TV3 202036-30, Instituto de Salud Carlos III PI 22/0031, RICORS40, Instituto de Salud Carlos III, Funded by EU-Next Generation, Mechanism of recuperation and resilience (MRR). K.I.S. is member of the *CKJ* editorial board.

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