НИРКИ ПОЧКИ KIDNEYS

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Hydration: the review of 3 trials

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Abstract. *The concepts of forced hydration and excessive forced hydration are discussed in the article. The authors emphasize that excessive forced hydration has a proven track record in improving the quality of life for dehydrated people. In case of normovolemia, there is no evidence of quality improvement and prolongation of life when excessive forced hydration is used. The issue of forced hydration in chronic kidney disease (CKD) is considered separately. Three randomized clinical trials were analyzed in which patients with CKD stage 1–2, 3 and 4–5 received forced hydration. The results of studies indicate the possible efficacy of forced hydration in stage 1–2 CKD in patients with normal or increased renal functional reserve. In stage 3 CKD, forced hydration showed no benefits, and in stage 4–5 CKD, it resulted in greater renal function loss. Summarizing these data, the authors concluded that it is probably appropriate for healthy people to consume the amount of fluid that provides physiological diuresis of 1.2–1.8 L and normal urine osmolarity. Forced hydration is often excessive, excessive forced hydration may not promote a healthy lifestyle. Forced hydration becomes excessive forced hydration as kidney function decreases. Possibly, the benefits of forced hydration are lost in CKD with progression of renal function loss. The effect of forced hydration for 12 months may be positive in stage 1 CKD and stage 2 CKD with normal renal functional reserve. Forced hydration is probably inexpedient in chronic stages 3–5.*

Keywords: *hydration; excessive hydration; excessive forced hydration; chronic kidney disease and hydration; renal functional reserve*

Nowadays, the issue of coaching to increase water intake (CIWI) is regarded as one of the elements of healthy lifestyle. Coaching to increase water intake was promoted by the formula of water amount for human intake: body weight × 30 × 1.5. For example, in a body weight of 60 kg: 60 × 30 × 1.5 = 2.700 mL. However, European Food Safety Authority (EFSA) recommends daily water intake of 1.6 L for women or 2.0 L for men and 2.000 mL (water and liquid) for women and 2.500 mL (water and liquid) for men living in a temperate climate and having normal physical activity [1]. Therefore, a certain controversy exists between coaching to increase water intake and excessive water intake.

International Society of Nephrology together with Danone has started the hydration initiative — ISN Hydration For Kidney Health Research [2]. For 10 years, hydration science has been actively used to make recommendations for water intake schedule [3]. Hydration For Health has provided several publications on hydration. Khan et al. were the first to show that increased water intake up to 2.5 L/day during 4 days significantly improves cognitive flexibility compared with low water intake (0.5 L/day) in children [4]. EFSA recommends that breastfeeding women should increase the amount of water for about 700 mL/day, i.e. appropriate intake is 2.700 mL/day (with food and drinks) or about 2.200 mL/day with drinks [5]. Hydration Calculator developed by Hydration for Health is available at https://www.hydrationforhealth.com/en/hydration-tools/hydration-calculator/. Almost all information of this entity is aimed at CIWI. However, it is important to distinguish water intake and liquid intake (water + liquid); high intake volumes refer directly to water and liquid from food.

Finally, excessive hydration has no definitive data in terms of its compliance, efficacy for increased life expectancy or improved quality of life. Certainly, hydration is beneficial in case of liquid deficiency that is commonly important for elderly people and athletes. Excessive hydration

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is effective for recurrent cystitis in premenopausal women, who drink a low amount of liquid [6]. An increase in water intake by 2 L (actually by 1.3 L) decreases the risk of crystallization in urine [7]. This is a well-known recommendation about preventive excessive hydration in people with urolithiasis; hydration for at least 2 L of diuresis is recommended for its prevention [8]. The key element is not an increase in liquid (water) intake by a certain volume, but obtaining the specified amount of urine. We believe that proper recommendations involve intake of the amount of liquid by healthy people that provides physiological diuresis of 1.2–1.8 L. At the same time, skilled approach outlines normal urine osmolarity. For example, if the urine is hyperosmolar, its amount is insufficient.

People with chronic kidney disease (CKD) is a specific population in terms of CIWI. Water excretory function of kidneys progressively decreases with the progression of CKD. Thus, a widespread recommendation of CIWI should probably be adjusted to CKD stage.

Currently, three randomized clinical trials of CIWI in CKD patients were conducted: The CKD WIT — Chronic Kidney Disease Water Intake Trial [9], ECIWIC — Early Coaching to Increase Water Intake in CKD [10], and HYD45 — Hydration in CKD 4–5 stages covering all 5 stages of CKD (Fig. 1).

ECIWIC, a prospective, multicenter, randomized trial in 4 parallel groups [10], was conducted among people with CKD stage 1–2 with/without CIWI, without low sodium chloride diet for 12 months. Hydration meant achievement of diuresis of 1.7–2 L. The primary outcome was a change in estimated glomerular filtration rate (eGFR), and secondary outcomes — albumin/creatinine ratio (ACR) in urine and quality of life (QoL) questionnaire (1–10, where 10 is the highest score of the QoL).

No statistically significant changes were achieved for eGFR in CKD G1 (95 mL/min/1.73 m^2 pre-hydration and 96 mL/min/1.73 m^2 in a year) and in CKD G2 (78 and 78 mL/min/m^2, respectively) in CIWI groups. In the groups without water loading, eGFR for CKD G1 was 96 and 93 mL/min/m^2, for CKD G2 — 76 and 73 mL/min/m^2, respectively (statistically insignificant reduction: $t = 0.6$, $p = 0.29$, $P \leq 0.05$). CIWI was accompanied by statistically insignificant, however, somewhat better quality of life.

Authors have tried to explain the reason for such changes. It turned out that the patients with high renal function reserve (RFR) (over 50 %) showed an increase in eGFR by 1.5 mL/min/m^2 in a year. Alternatively, people with low reserve demonstrated a decrease in eGFR by 1.1 mL/min/m^2 with CIWI. ACR also directly correlated with high renal function reserve.

CKD WIT, a randomized, clinical, parallel-group trial, was conducted in patients with CKD G3 in two groups during 12 months. Those on forced hydration had diuresis higher by 0.6 L. Mean change in eGFR was –2.2 mL/min/1.73 m^2 in hydration group and –1.9 mL/min/1.73 m^2 in the control group (adjusted difference between the groups was –0.3 mL/min/1.73 m^2 (95% confidence interval –1.8 to 1.2; $p = 0.74$)).

HYD 45, a randomized, prospective, parallel-group trial, was aimed at evaluation of eGFR with achievement of higher diuresis, minimally by 400 mL, in 20 patients with CKD G4–5 with and without CIWI. Stated duration was 12 months, and the trial was terminated in 6 months due to a more pronounced drop in eGFR in CIWI group, namely: –3.3 vs. 2 mL in the group without CIWI (data on file).

Comparison of the obtained results in the mentioned trials is provided in Table 1.

There is no statistical significance between renal function loss in CIWI and without it ($p = 0.367$, Student's t-test is –1.059). However, the total loss of kidney function by eGFR without hydration is somewhat higher (negative trend). Analysis of the obtained data suggests that CIWI is effective only for CKD G1 and in people with preserved renal function reserve. In CKD G2, CIWI has no significant effect on eGFR, while people without CIWI have reduced glomerular filtration (–3 mL/min). With renal function worsening, CIWI accelerates impairment of re-

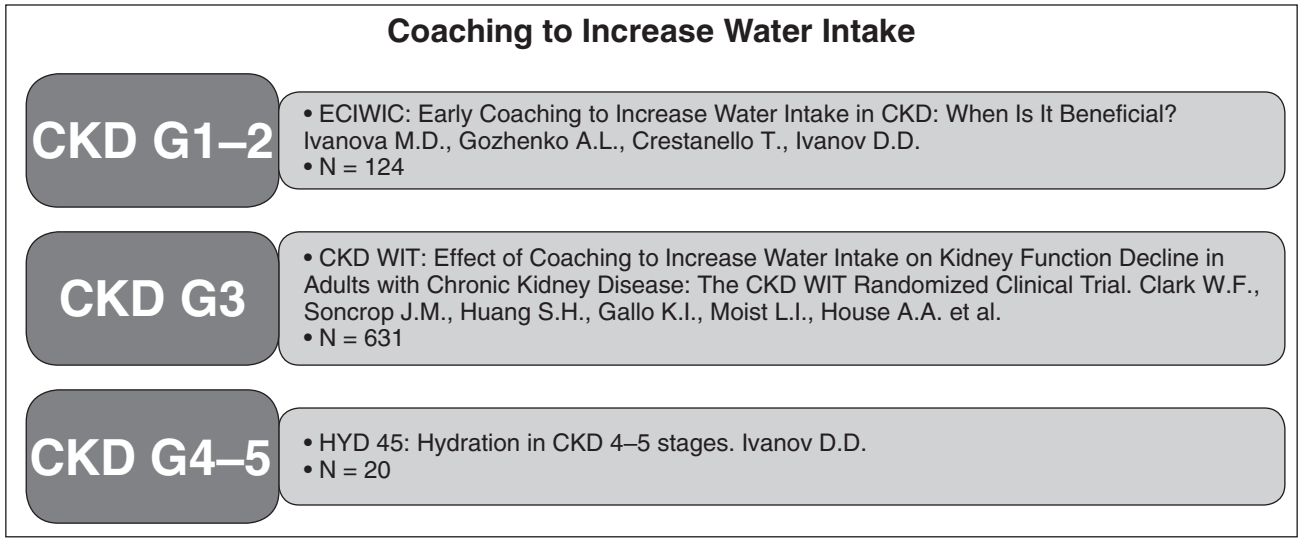

Figure 1. Clinical trial of CIWI in CKD

Table 1. Changes in eGFR in CKD G1–5 (mL/min/m²)

Intervention	CKD			
	G1	G2	G3	G4–5
With CIWI	+1	0	–2.2	–3.3
Without CIWI	–3	–3	–1.9	–2

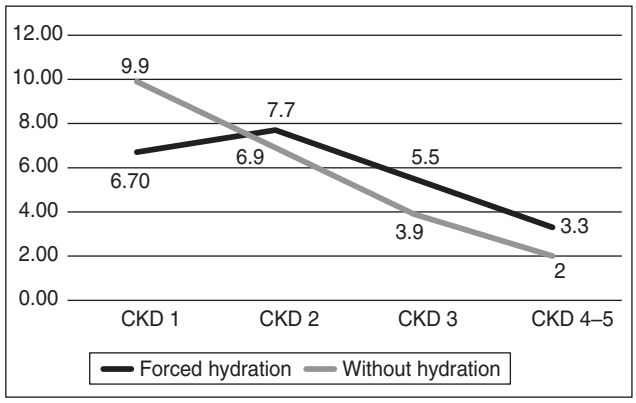

Figure 2. Dynamics of eGFR (ml/min/m³) within a year with/without hydration

nal function by eGFR within the range of CKD G3–5 at the rate of –5.3 vs. –3.9 mL/min without CIWI. Probably, high RFR allows manifestations of beneficial effects of CIWI [11].

Therefore, with CKD G1, the CIWI leads to the preservation of the renal function with eGFR increase of 1 mL/min/m² per year. In CKD G2, CIWI prevents physiological and pathological loss of renal function, RFR above 50 % helps restore eGFR even in CKD G1–2. ECIWIC trial demonstrates benefit of CIWI primarily in patients with CKD 1–2 and preserved RFR. CKD WIT suggests neutral effect of CIWI with a tendency towards negative effect in CKD. HYD 45 demonstrates negative effect of CIWI in CKD G4–5.

Conclusions

1. Proper recommendations involve intake of the amount of liquid that provides physiological diuresis of 1.2–1.8 L and normal urine osmolarity.

2. CIWI is commonly excessive and does not contribute to a healthy lifestyle.

3. CIWI becomes excessive with the worsening of renal function. Benefits of CIWI are possibly lost in CKD with progressive worsening of renal function.

4. Positive effect of CIWI during 12 months may be positive in CKD G1 and CKD G2 with high RFR.

5. Probably, CIWI is inadvisable in CKD G3–5.

Conflicts of interests. M.D. Ivanova presented ECIWIK research in 2019 in France at the H4H conference.

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Водне навантаження: огляд трьох РКД

Резюме. У статті розглянуті поняття примусової гідратації і надмірної примусової гідратації. Автори акцентують увагу на тому, що примусова надмірна гідратація має доказову базу в покращенні якості життя в зневоднених осіб. При нормоволемії доказових даних про підвищення якості і подовження тривалості життя при застосуванні примусової надмірної гідратації немає. Окремо розглянуто питання примусової гідратації при хронічній хворобі нирок (ХХН). Проаналізовані три рандомізовані клінічні дослідження, в яких пацієнти з ХХН 1–5-ї стадій отримували примусову гідратацію. Результати досліджень свідчать про можливу ефективність примусової гідратації при ХХН 1-ї та 2-ї стадій, що відмічається в пацієнтів із нормальним або підвищеним функціональним нирковим резервом. При ХХН 3-ї стадії примусова гідратація не показала переваг, а при ХХН 4-ї та 5-ї стадій примусова гідратація призводила до більшої втрати функції нирок. Узагальнюючи наведені дані, автори дійшли висновку, що здоровим особам, імовірно, доцільно вживати ту кількість рідини, що забезпечує фізіологічний діурез 1,2–1,8 л і нормоосмолярність сечі. Примусова гідратація нерідко є надмірною. Примусова надмірна гідратація, можливо, не сприяє здоровому образу життя. Примусова гідратація стає примусовою надмірною гідратацією при зниженні функції нирок. Імовірно, переваги примусової гідратації втрачаються при ХХН із прогресуванням втрати функції нирок. Ефект примусової гідратації протягом 12 місяців може бути позитивним при ХХН 1-ї та 2-ї стадій із нормальним функціональним нирковим резервом. Примусова гідратація, імовірно, недоцільна при ХХН 3–5-ї стадії.

Ключові слова: гідратація; надмірна гідратація; примусова надмірна гідратація; хронічна хвороба нирок і гідратація; функціональний нирковий резерв

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Гидратация: обзор трех РКИ

Резюме. В статье рассмотрены понятия принудительной гидратации и чрезмерной принудительной гидратации. Авторы акцентируют внимание на том, что принудительная чрезмерная гидратация имеет доказательную базу в улучшении качества жизни у обезвоженных людей. При нормоволемии доказательных данных о повышении качества и продолжительности жизни при использовании принудительной чрезмерной гидратации нет. Отдельно рассмотрен вопрос принудительной гидратации при хронической болезни почек (ХБП). Проанализированы три рандомизированных клинических исследования, в которых пациенты с ХБП 1–5-й стадии получали принудительную гидратацию. Результаты исследований свидетельствуют о возможной эффективности принудительной гидратации при ХБП 1-й и 2-й стадий, которая отмечается у пациентов с нормальным или повышенным функциональным почечным резервом. При ХБП 3-й стадии принудительная гидратация не показала преимуществ, а при ХБП 4-й и 5-й стадий принудительная гидратация приводила к большей потере функции почек. Обобщая приведенные данные, авторы пришли к выводу, что здоровым людям, вероятно, целесообразно употреблять то количество жидкости, которое обеспечивает физиологический диурез 1,2–1,8 л и нормоосмолярность мочи. Принудительная гидратация нередко является чрезмерной. Принудительная чрезмерная гидратация, возможно, не способствует здоровому образу жизни. Принудительная гидратация становится принудительной чрезмерной гидратацией по мере снижения функции почек. Вероятно, преимущества принудительной гидратации теряются при ХБП с прогрессированием утраты функции почек. Эффект принудительной гидратации в течение 12 месяцев может быть положительным при ХБП 1-й и 2-й стадий с нормальным функциональным почечным резервом. Принудительная гидратация, вероятно, нецелесообразна при ХБП 3–5-й стадии.

Ключевые слова: гидратация; чрезмерная гидратация; принудительная чрезмерная гидратация; хроническая болезнь почек и гидратация; функциональный почечный резерв