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STATUS OF HEMOSTATIC SYSTEM IN MEN WITH UROLITHIASIS TREATED UNDER DURING COVID-19 PANDEMIC

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Abstract. ***Introduction.*** Androgen replacement therapy has been shown to be effective in the treatment of patients with urolithiasis and androgen deficiency. ***The aim of the work*** was to find out whether androgen replacement therapy is applicable in the treatment of patients with androgen deficiency in the specific conditions of the COVID-19 pandemic with regard to its possible influence on the most important link in the pathogenesis of COVID-19 — blood coagulation. ***According to the results*** of hospital treatment of 199 men suffering from urolithiasis, it was found that androgen replacement therapy is not an obstacle for therapeutic measures aimed at persistent restriction of coagulation processes. ***Conclusion.*** In case of pandemic recurrence, androgen replacement therapy can be used in the treatment of urolithiasis.

Keywords: urolithiasis, hemostasis, androgen therapy, COVID-19

СОСТОЯНИЕ СИСТЕМЫ ГЕМОСТАЗА У МУЖЧИН, БОЛЬНЫХ УРОЛИТИАЗОМ, ПРОХОДИВШИХ ЛЕЧЕНИЕ В УСЛОВИЯХ ПАНДЕМИИ COVID-19

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Резюме. ***Введение.*** Андрогенная заместительная терапия показала свою эффективность в лечении больных с мочекаменной болезнью и андрогенным дефицитом. **Целью работы** было выяснить, применима ли андрогенная заместительная терапия в лечении больных с андрогенным дефицитом в специфических условиях пандемии COVID-19 в том, что касается ее возможного влияния на важнейшее звено патогенеза COVID-19 — процессы свертывания крови. **По результатам** стационарного лечения 199 мужчин, страдающих уролитиазом, установлено, что андрогенная заместительная терапия не является препятствием для проведения лечебных мероприятий, направленных на стойкое ограничение коагуляционных процессов. **Вывод.** У больных, страдающих от инфекции COVID-19 и одновременно получающих андрогенную заместительную терапию как часть лечения уролитиаза, достижимо стойкое ограничение коагуляционных процессов, и андрогенная заместительная терапия препятствием для этого не является. В будущем, в случае повторения пандемии, андрогенная заместительная терапия может быть применена в лечении уролитиаза.

Ключевые слова: мочекаменная болезнь, гемостаз, андрогенная терапия, COVID-19

INTRODUCTION

Androgen replacement therapy has shown its effectiveness in the treatment of patients with urolithiasis and androgen deficiency [4–6]. The pandemic of a new coronavirus infection has made adjustments in the use of a significant part of treatment methods for a wide range of diseases.

Articles published by urologists in scientific journals during the coronavirus pandemic focus more or less on organizational issues: the impact of reduced physical activity during the pandemic on the course of urolithiasis [10]; impact of drug treatment of nephrolithiasis on the efficacy of COVID-19 vaccination [20]; assessment of the burden on urologic units during the pandemic [11, 12]; management of urologic units in this setting [19]; triage of patients [8, 9, 13] and, in particular, the possibility of postponing surgical treatment until after the pandemic [17]; methods of preoperative assessment of patients and the choice of anesthetic techniques to provide urological operations [15]; risk of postoperative complications [16] and the quality of life of patients undergoing surgical treatment for nephrolithiasis in pandemic conditions [23].

The pathophysiology of urolithiasis complicated by coronavirus infection remains practically unstudied in the world. The influence of androgen deficiency and, even more so, the effectiveness of androgen replacement therapy, carried out against the background of a new coronavirus infection, are not considered.

At the same time, disturbances in the blood coagulation system — an increase in coagulation, endothelial inflammation, suppression of fibrinolysis are known as one of the main manifestations of COVID-19 infection [1, 2, 7, 21]. Does androgen replacement therapy have an effect on these processes? Literature data on this issue are extremely scarce.

A study of the blood coagulation system in elderly men showed a negative correlation between plasma testosterone levels and blood platelet reactivity [18]. Androgens reduce the activity of coagulation processes [14]. Their long-term use can have antithrombotic effect [24]. One of the reasons for the decrease in the activity of fibrinolysis is the increased production of PAI-1, a plasminogen activator inhibitor. However, at the same time, exogenous androgens inhibit PAI-1 and thus increase fibrinolysis [22].

AIM

To clarify whether androgen replacement therapy is applicable in the treatment of androgen-deficient patients under the specific conditions of the COVID-19 pandemic with regard to its possible effects on the coagulation processes.

MATRIALS AND METHODS

The organization of clinical studies. Laboratory tests were performed in accordance with standard methods in the laboratory department of the State Budgetary Institution “Elizavetinskaya Hospital” (St. Petersburg). The study included 199 men aged from 25 to 68 years who were patients of the urological unit (the head of the unit is Dr. N.S. Tagirov). Most of the parameters were recorded four times: at the time of the beginning of inpatient treatment, at the time of its completion, in 4 months and 1 year after its completion. Some parameters were registered three times: at the moment of the beginning of inpatient treatment, after 4 months and after 1 year. One half of the patients (100 patients) received androgen replacement therapy, the other half (99 patients) received conventional therapy (contact lithotripsy performed after the extracorporeal shock wave lithotripsy). The method of androgen replacement therapy was previously described by the head of the collective [5, 6].

Statistical analysis of the results. We used the program packages SPSS for Windows and STATISTICA v. 6.0. The significance of intergroup differences was assessed by nonparametric methods: Mann–Whitney U-test, Wilcoxon criterion and ANOVA with Bonferroni correction [3].

RESULTS

Platelets. During the whole observation period, the average number of platelets in COVID– and COVID+ groups (Fig. 1) ranged from 290±35 to 319±54 × 10^9/l and did not differ statistically significantly ($p > 0.05$). In all patients, regardless of the type of therapy, the dynamics of the index was similar: no changes were observed during the treatment ($p > 0.05$). A statistically significant decrease in platelet count ($p < 0.001$) to 270±31 to 279±36 × 10^9/l was observed by 4 months and remained at the same level up to 1 year.

Fibrinogen. The mean fibrinogen concentration in the blood of COVID– patients was near the upper limit of normal (2.0-3.9 g/L) from the beginning of hospital treatment and up to 1 year afterward (Fig. 2). Fibrinogen concentration decreased in COVID+ patients and by 4 months was 4.05±0.84 g/L ($p< 0.001$) with conventional treatment and 2.07±0.36 ($p < 0.001$) with androgen replacement therapy. COVID+ patients receiving androgen replacement therapy had 1.74 g/L ($p < 0.001$) lower plasma fibrinogen concentration by 1 year than the COVID- group. Among patients receiving conventional therapy, the fibrinogen concentration in the COVID+ group was 0.64 g/L higher ($p < 0.05$) than in the COVID– group.

D-dimer. In COVID– patients, the mean level of this parameter did not change significantly during the study; there were changes in the range of 212±44 to 250±63 ng/L (Fig. 3). D-dimer levels

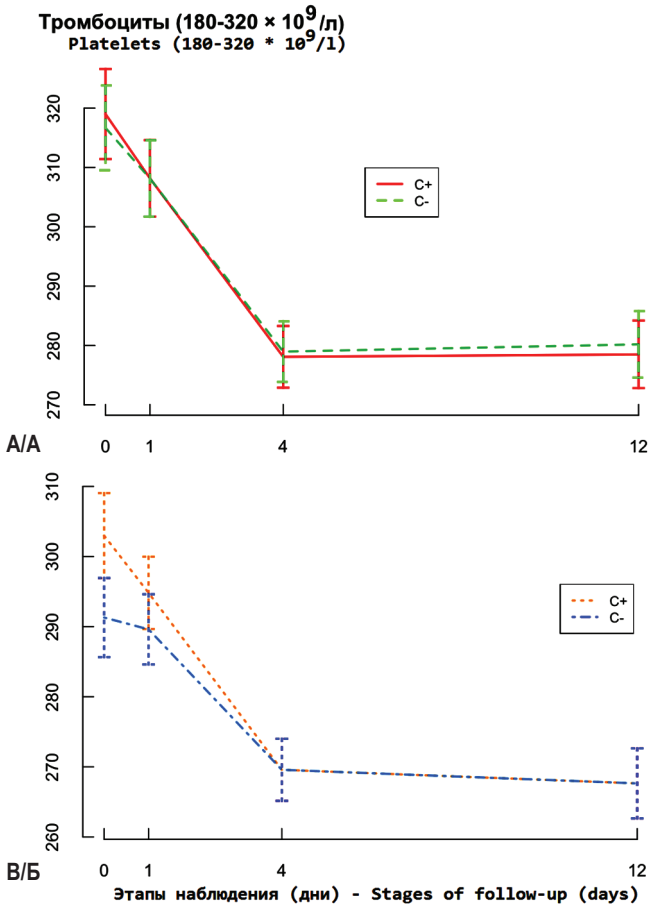

Fig. 1. Number (×10⁹/l) of platelets in the blood of patients who received traditional treatment (A) or androgen replacement therapy (B) for urolithiasis: C+ — with COVID-19; C– — without COVID-19. Stages of follow-up: 0 — at the beginning of treatment; 1 — at the time of hospital discharge; 4 — after 4 months; 12 — after 12 months. Mean ± standard deviation are presented

Рис. 1. Количество (×10⁹/л) тромбоцитов в крови больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Этапы наблюдения: 0 — начало стационарного лечения; 1 — окончание стационарного лечения; 4 — через 4 месяца; 12 — через 12 месяцев. Представлены средние арифметические ± среднеквадратическое отклонение

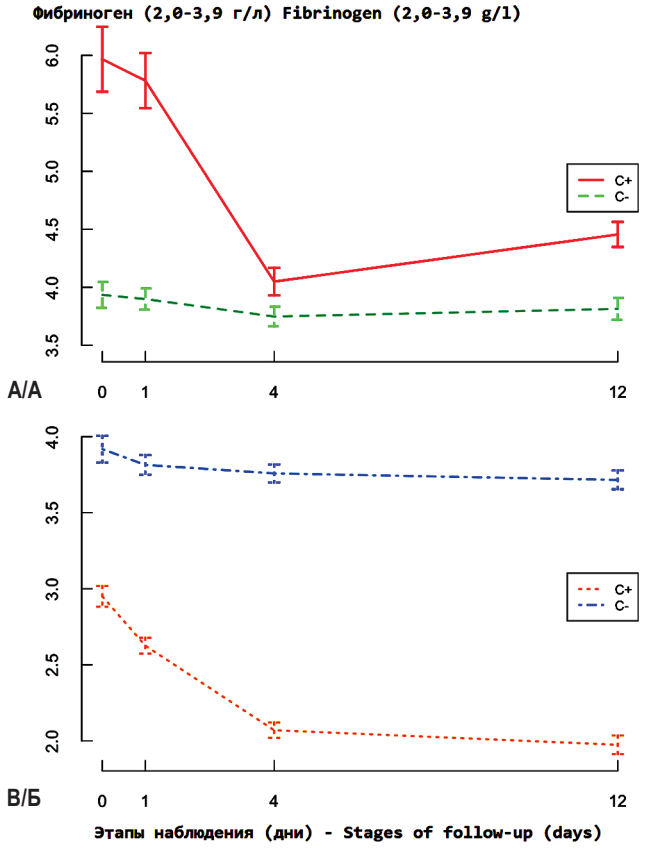

Fig. 2. Fibrinogen levels (g/L) in the blood of patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 2. Уровень фибриногена (г/л) в крови пациентов, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

were 412±163 to 398±91 ng/L in COVID+ patients at the time of treatment initiation. The level remained virtually unchanged during conventional treatment, but decreased to 282±70 ng/L after 4 months ($p < 0.001$) and to 231±26 ($p < 0.001$) after 1 year. In the case of androgen replacement therapy, the decrease in D-dimer levels to 68 ng/L ($p < 0.01$) occurred during hospitalization. By 4 months the decrease reached 124 ng/L ($p < 0.001$), after 1 year the index remained at the same level.

Activated partial thromboplastin time (aPTT). The mean value of aPTT at the beginning of hospital treatment ranged from 28.4±2.3 to 40.0±13.8 s (Fig. 4). In the COVID– group, the index decreased by 1.53-2.00 s during treatment ($p < 0.05$). APTT dynamics in COVID+ patients depended on the applied treatment. The index first increased by 2.70 s ($p < 0.05$) during androgen replacement therapy, then decreased to the baseline level. The decrease in the conventional therapy group was observed within 4 months and amounted to 8.2 s ($p < 0.05$). Later aPTT was at the same level. In general (except for the moment of hospitalization completion) aPTT in COVID+ patients was lower than in COVID- patients under androgen replacement therapy and higher under conventional therapy.

International normalized ratio (INR). At the time of inpatient treatment, the mean INR ranged from 1.19±0.23 to 1.54±0.60 (Fig. 5). INR remained at the same level or increased in the group receiving only conventional therapy and decreased in the group receiving androgen replacement

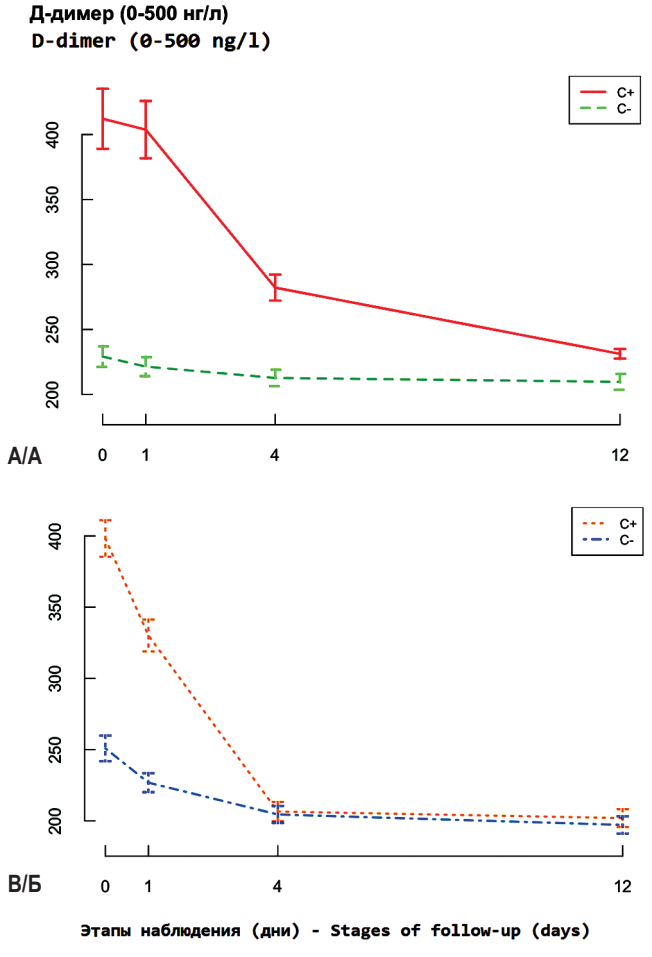

Fig. 3. D-dimer level (ng/L) in plasma of patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 3. Уровень D-димера (нг/л) в плазме крови больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

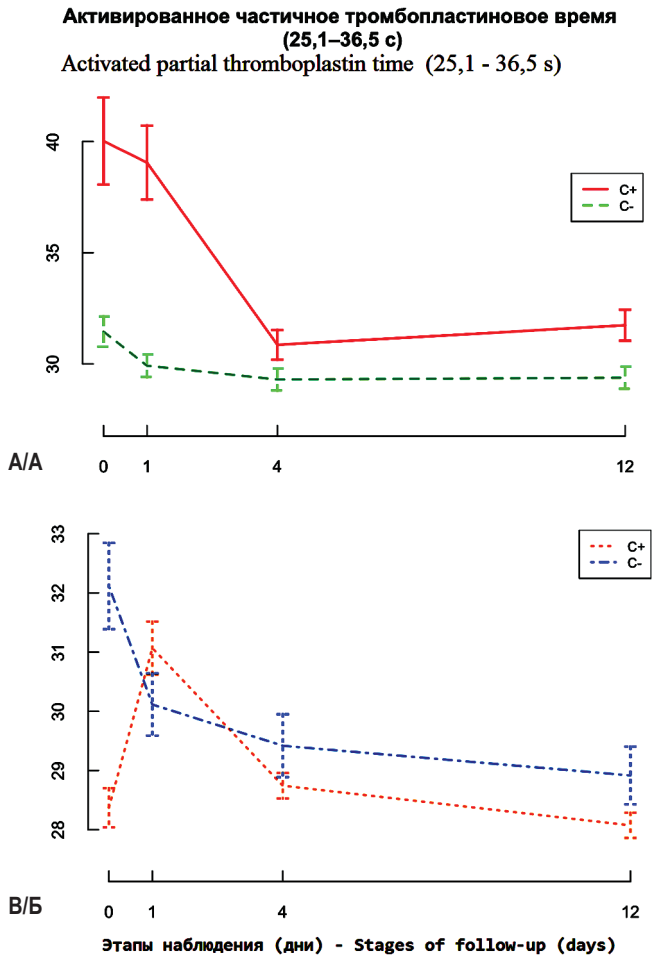

Fig. 4. Activated partial thromboplastin time (c) recorded in patients receiving conventional treatment (A) or androgen replacement therapy (B) for urolithiasis: C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 4. Активированное частичное тромбопластиновое время (с), зарегистрированное у больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

therapy during the treatment of COVID+ patients. androgen replacement therapy. By 4 months INR stabilized in the range of 1.13±0.39 to 1.21±0.17, and by 1 year there were no significant changes. The index was 1.07±0.23 to 1.19±0.47 units by the end of follow-up. Differences between COVID+ and COVID– groups were statistically significant only during the treatment period and by the time of hospital discharge, which was 0.23–0.40 units ($p < 0.01$).

DISCUSSION

Platelets. The platelet count (Fig. 1) was within the normal range (180–320×10^9/l) during the observation period and underwent similar changes: a decrease during treatment and by 4 months, later the maintenance at the same level. The dynamics of the parameter was not related to the type of urolithiasis treatment, nor to the presence or absence of COVID-19 infection. According to this indicator, new coronavirus infection is not a contraindication for treatment of urolithiasis in general and androgen replacement therapy in particular.

Fibrinogen. The amount of fibrinogen (Fig. 2) in the blood of COVID+ patients decreased sharply during treatment and in the first time after discharge from the hospital, and by 4 months it was equal to the index in the group of patients who did not suffer from a new

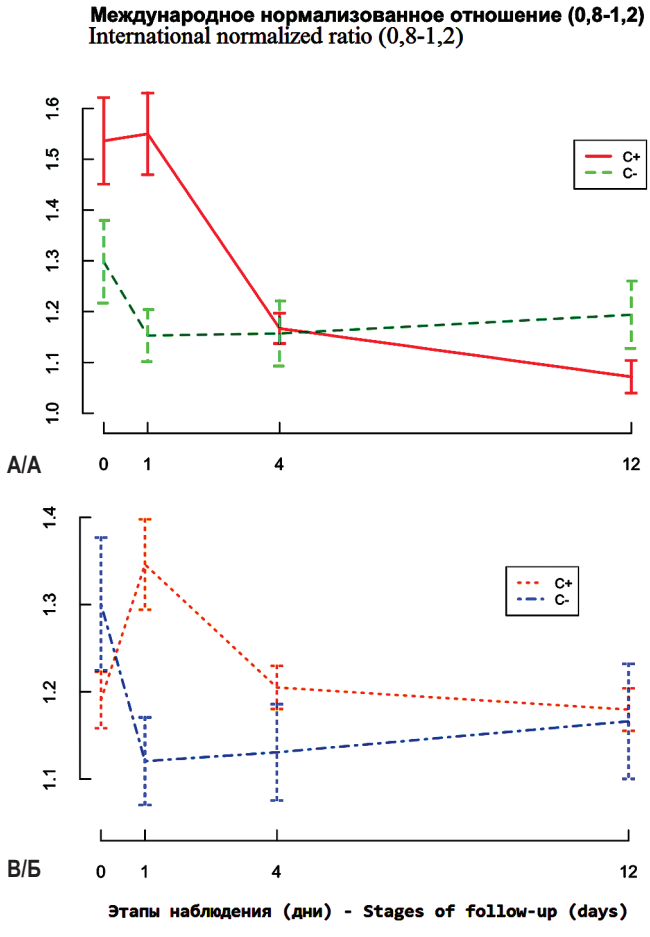

Fig. 5. **International normalized ratio recorded in patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — indicates with COVID-19; C– — indicates without COVID-19. Other designations are the same as in Fig. 1**

Рис. 5. **Международное нормализованное отношение, зарегистрированное у больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1**

coronavirus infection. While baseline values differed, the dynamics of the index was not related to the type of treatment for urolithiasis. We consider these results as confirmation that androgen replacement therapy used as a component of treatment of urolithiasis is not an obstacle to attenuation of coagulation processes in patients suffering from the concurrent COVID-19 infection.

D-dimer. This indicator of fibrinolysis (Fig. 3) was within the normal range (from 0 to 500 ng/L) in all patients. The difference between COVID+ and COVID– groups leveled out by 4 months in case of androgen replacement therapy, while in case of conventional therapy it disappeared only by 1 year. We believe that the coagulation restriction used in COVID-19 is also not a contraindication for androgen replacement therapy in the treatment of urolithiasis.

Activated partial thromboplastin time. We registered multidirectional changes in aPTT (Fig. 4). Significant differences between the values of this index in COVID+ and COVID– patients were noted in the course of treatment, but only in patients receiving conventional therapy.

International normalized ratio. In COVID+ patients receiving androgen replacement therapy, INR increased by 0.16 units during treatment ($p < 0.05$), indicating coagulation limitation (Fig. 5). The index did not differ by 4 months between patients who had suffered from coronavirus infection and those who had avoided coronavirus infection. We consider these data as another indication that it is possible to treat COVID-19 infection and urolithiasis simultaneously, including with the use of androgen replacement therapy.

CONCLUSION

In patients suffering from COVID-19 infection and concomitantly receiving androgen replacement therapy as part of the treatment of urolithiasis, sustained coagulation limitation is achievable, and androgen replacement therapy is not a barrier to this. In the future, if the pandemic recurs, androgen replacement therapy may be used in the treatment of urolithiasis.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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