Winter 2026, Volume 11, Issue 40 (8- 15) DOI: 10.22034/ppmj.2026.735667

Personalized & Precision Medicine Journal

Homepage: www.pmjournal.ir

Pituitary hormones Profile, Cholesterol Levels, and Steroidogenic Genes Expression are Useful Information in Prostate Cancer

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ARTICLE INFO

Paper Type: Original Article

Submitted: 2025-10-13
Accepted: 2026-02-28

Keywords:
Prostate Cancer
Androgens
Testosterone
Cholesterol
Pituitary Hormones

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ABSTRACT

Objective: To investigate the relationship between changes in the level of Pituitary hormones, cholesterol levels, and the expression of genes involved in the biosynthesis of androgens, this study was designed.

Methods: In this study, the amount of changes in the levels of LH, FSH, and PRL hormones, as well as the level of cholesterol as a precursor of androgens, LDL and HDL lipoproteins, and the expression level of two genes, CYP17A1 and CYP11A1, in 120 people with prostate cancer as a case group and 120 people with BPH as a control group by RT-qPCR.

Results: The statistical analysis demonstrated that serum levels of testosterone, LH, and TSH were significantly higher in the malignant group compared to the benign group. PRL levels were also elevated in the Prostate cancer (PCa) group; however, this difference did not reach statistical significance. No significant difference was observed in serum PSA levels between the two groups. Prostate volume was significantly greater in the benign group than in the malignant group. Serum cholesterol levels were significantly higher in the PCa group compared to the Benign prostatic hyperplasia (BPH) group. In contrast, serum levels of LDL and HDL lipoproteins showed no significant differences between the groups. Additionally, the expression levels of CYP11A1 and CYP17A1 genes were significantly increased in the PCa group relative to the BPH group.

Conclusion: The results of this study showed that monitoring the hormonal profile and cholesterol level can play an important role in predicting the course of the disease.

How to Cite this Article:

Gh. Gh. V. Zaghard, M. Haghi, M. Ghiamirad, S. Ghorbian, M. Ebrahimi "Pituitary hormones Profile, Cholesterol levels, and steroidogenic genes expression are useful information in Prostate Cancer" Personalized & Precision Medicine Journal, Vol. 11, no. 40, pp. 8- 15.

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed malignancy and the sixth leading cause of cancer-related mortality among men worldwide. The global burden of this disease is projected to reach nearly 2.3 million new cases (1). Age-related enlargement of the prostate, known as Benign prostatic hyperplasia (BPH), is commonly associated with symptoms such as polyuria in men over 60 years of age (2). Owing to similarities in histopathological and molecular features, BPH is regarded as a potential stage in the initiation of prostate tumors; however,

the precise mechanisms underlying the progression from BPH to prostate cancer remain unclear (3-4). The incidence of PCa is higher in developed countries, largely due to the widespread use of prostate-specific antigen (PSA) testing for diagnosis (5). Advances in medical science in recent years, particularly in developed regions, have led to notable improvements in patient survival and prognosis. Major risk factors for prostate tumor development include age, race, genetic background, family history, obesity, and smoking (6). When treatment fails, PCa may progress to Castration-resistant prostate cancer (CRPC), which represents a significant clinical challenge (7).

Androgens are essential for the growth of PCa. They stimulate proliferation in both normal and malignant prostate cells through binding to and activating the androgen receptor (AR), a protein expressed in these cells (8). AR functions as a steroid receptor transcription factor for testosterone and dihydrotestosterone (DHT) and belongs to the nuclear receptor superfamily, sharing structural similarities with the estrogen, progesterone, glucocorticoid, and thyroid hormone receptors (9). Overexpression of AR allows PCa to progress even at castration levels of androgens. Tumor cells with AR amplification can persist during androgen deprivation therapy and advance to Castration-resistant prostate cancer (CRPC) (10).

Testosterone and dihydrotestosterone are the predominant androgens in men. Circulating testosterone levels are correlated with PSA levels, Gleason score, and AR expression in newly diagnosed PCa patients. In a retrospective study, men with low baseline testosterone exhibited reduced levels of LH, FSH, and estradiol, along with lower PSA levels, but a higher mean Gleason score. In these individuals, AR expression was elevated compared to groups with normal or high testosterone levels (11). AR demonstrates high affinity for both testosterone and 5α-dihydrotestosterone (DHT), which serve as its principal physiological ligands. The majority of circulating testosterone in healthy adult males is produced by the testes, while approximately 5–10% originates from the adrenal glands (12).

PCa cells are also capable of synthesizing small amounts of testosterone directly from cholesterol via sequential enzymatic activity involving CYP11A1, CYP17A1, HSD3B1 or HSD3B2, and AKR1C3, through a pathway typically active in the adrenal glands and testes (13). Previous studies have suggested that cholesterol biosynthesis may be elevated in CRPC (14-15); however, whether CRPC cells can generate physiologically meaningful levels of androgens de novo from cholesterol remains unclear. Investigations, primarily in LNCaP cells and xenograft models, have shown that key enzymes required for de novo steroidogenesis, including CYP11A1 and CYP17A1, are expressed and may be upregulated in castration-resistant sublines (16-17).

FSH and LH are produced by the pituitary gland. It's located at the base of your brain, and it's responsible for many functions in the body. FSH is necessary for sperm production (spermatogenesis). LH stimulates the production of testosterone, which is necessary to continue the process of spermatogenesis (18). Several studies have implicated dysregulation of the FSH and luteinizing hormone (LH) system as a whole in both the initial development and progression of prostate cancer, and the development of CRPC (19). Testosterone is produced from cholesterol in testicular Leydig cells under the regulation of pituitary gonadotropin LH; accordingly, several studies have reported an association between cholesterol levels and the risk of Prostate cancer (20-21). Hormonal markers may also be applied alongside prostate-specific antigen to improve its predictive performance (22).

In the present study, serum levels of testosterone, LH, FSH, prolactin, and cholesterol were assessed in individuals with prostate cancer and Benign prostatic hyperplasia. Since CYP11A1 and CYP17A1 enzymes play roles in testosterone biosynthesis from cholesterol, their expression levels were examined in patients with prostate cancer and benign prostatic hyperplasia. Furthermore, the association between changes in the expression of these genes and the levels of LH and FSH hormones, as well as cholesterol as a precursor, was analyzed. This study aimed to investigate the relationship between hormonal profile, cholesterol levels, and alterations in the expression of genes involved in the androgen synthesis pathway in patients with prostate cancer and benign prostatic hyperplasia.

MATERIALS AND METHODS

The population studied in this research included 120 people with prostate cancer and 120 people with benign prostatic hyperplasia, referred to Khatam Al-Anbia Hospital in Tehran between 2020 and 2021. After receiving informed consent from the patients, their information and files were received from the hospital. The conditions for entering the study were having a pathology confirmation based on benign and malignant prostate hyperplasia, as well as having a complete list of hormonal tests before receiving any medication. Also, in order to investigate the changes in CYP11A1 and CYP17A1 gene expression, a FFPE block was obtained from the prostate tissue in the pathology department of the hospital. All samples were taken from patients before the start of treatment.

Hormonal information, including total testosterone level, Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), prolactin (PRL), histopathological information, including prostate size, tumor stage, Gleason score, demographic information, including

patient age, marital status, and education. Also, the levels of prostate surface antigen, cholesterol, LDL, and HDL were collected.

Then, the RT-qPCR method was used to investigate the changes in the expression of the androgen receptor (AR) gene and the relationship between the expression changes of this gene and hormonal, biochemical, and pathological factors. For this purpose, RNA extraction from FFPE section was performed as previously described (22), Briefly, under appropriate conditions, tissue samples were deparaffined by xylene, then protein digestion was performed by proteinase K and its buffer (Tris-HCl 100mM + NaCl 200mM + EDTA 2mM + SDS1%). After that, 1 mL Trizol solution was added to samples. Continue the steps according to the manufacturer's instructions. RNA samples were quantified using a spectrophotometer and then subjected to electrophoresis on a 1.5% agarose gel to assess RNA integrity. Reverse transcription was performed using the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, cat. K1622) according to the manufacturer's protocol.

Expression levels of the gene were measured by real-time PCR using the RealQ Plus 2x Master Mix Green (Ampliqon, Denmark). Real-time PCR was carried out on a RotorGene Q real-time PCR system (Qiagen, Germany). Signals were normalized to the "house-keeping" gene GAPDH as an endogenous internal control. Primer sequences were used include: CYP17A1 forward primer: 5'-CCGTAAGGGTATCGCCTTCG-3', CYP17A1 reverse primer: 5'-CCATCCTTGAACAGGGCAAAG-3' (NM_000102.4); CYP11A1 forward primer: 5'-GCTGAAGTGGAGCAGGTACA-3', CYP11A1 reverse primer: 5'-CTTTGACCAGGACTGAGCGT-3'(NM_000781.3) and GAPDH forward primer: 5'-GTCTCCTCTGACTTCAACAGCG-3', GAPDH reverse prime:5'-ACCACCCTGTTGCTGTAGCCAA-3' (NM_002046.7). The optimal annealing temperature for each primer pair was established prior to analyzing the experimental samples. Real-time PCR reactions were performed in triplicate for each sample. The mean Ct values obtained from each reaction were normalized against GAPDH. Relative gene expression levels were then determined using the 2^-ΔΔCt method.

All statistical analyses were conducted using SPSS for Windows, version 26.0 (IBM, SPSS, Chicago, IL, USA). Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Comparisons between the two groups were performed using the Mann–Whitney U test. Correlations were evaluated using Pearson's correlation coefficient for continuous variables and Spearman's correlation coefficient for ordinal and discrete variables.

RESULTS

The population studied in this research includes 120 people with prostate carcinoma and 120 people with benign prostatic hyperplasia. The demographic characteristics these patients are shown in Supplementary Table 1. As shown, the malignant and the benign groups were well matched according to age (median 61.45 years for the malignant group and 66.4 years for benign group) In the comparison between the two groups, no significant relationship with age was reported $p>0.05$. In the benign group, 118 people were married and only 2 people were single, and in the benign group, 116 people were married and only 4 people were single, $p>0.05$. In terms of education level, no significant relationship was reported between the two groups $p>0.05$ (The details of the level of education in the two groups can be found in supplementary Table 1).

The levels of testosterone, LH, TSH and prolactin hormones in the serum of the two groups were compared as shown in Table 1. The serum testosterone level was significantly higher in the benign group compared to the malignant group (mean level in BPH was 428.01 ng/dl, compared with PCa 382.84 ng/dl, $p<0.05$). The level of LH (6.14 mIU/ml in PCa Vs. 5.12 mIU/ml in BPH; $p<0.05$) and TSH (7.96 mIU/ml in PCa Vs 6.82 mIU/ml in BPH; $p<0.05$) in the malignant group was significantly higher than the benign group. The PRL level was also higher in the PCa group (8.18 ng/ml) than in the BPH group (97.98 ng/ml) but this difference was not statistically significant ($p>0.05$).

As can be seen in Supplementary Table 2, no significant difference was observed in serum PSA level in the two groups (level means in PCa 6.34 Vs. 6.89 ng/ml in BPC; $p>0.05$). The prostate volume was compared in the groups; it was significantly larger in the benign group than in the malignant group (55.37 ml in BPH Vs 47.07 ml in PCa; $p<0.05$).

Also, as can be seen in Supplementary Table 3, the level of LH in stage II of the disease is higher than in stage III, and the level of FSH in stage III is higher than in stage II. However, no significant changes were observed between testosterone and prolactin levels in stage II and III of the disease.

Cholesterol level as one of the precursors of testosterone synthesis, was also measured in two groups; as can be seen in Table 2, the level of serum cholesterol was significantly higher in the PCa group than in the BPH group (level means in PCa 217.5 Vs. 189.8 mg/dl in BPC; $p<0.05$). Also, the levels of LDL (level means in PCa 94.2 Vs. 90. 3 mg/dl in BPC; $p>0.05$) and HDL (level means in PCa 49.02 Vs. 45.87 mg/dl in BPC; $p>0.05$) lipoproteins in the

Table 1. The relationship between patients› demographic information and the occurrence of benign prostatic hyperplasia (BPH) and prostate carcinoma.

parameters	BPH (mean±SD)	Pca (mean±SD)	Sig ≤0.05*
Testosterone	428.01 (56.19)	382.84 (81.67)	**<0.05**
LH	5.12 (0.58)	6.14 (0.81)	**<0.05**
FSH	6.82 (0.81)	7.96 (0.53)	**<0.05**
PRL	7.98 (0.53)	8.18 (0.76)	>0.05

*Mann-Whitney U test. Testosterone normal range: 300-1000 ng/dl. LH normal range: 20-70 yeas between 1.3-8.0 mIU/ml. FSH normal range: between 1.5-12.4 mIU/ml. PRL normal range: between 2-17 ng/ml

Table 2. Evaluation of the relationship between prostate volume indices and PSA levels with benign prostatic hyperplasia and prostate carcinoma.

Parameters	BPH (mean±SD)	Pca (mean±SD)	Sig ≤0.05*
cholesterol	189.8 ± 36.85	217.5 ± 46.97	**<0.05**
LDL	90.3 ± 11.23	94.2 ± 10.91	>0.05
HDL	45.87 ± 10.10	49.02 ± 8.89	>0.05

*Mann-Whitney U test. Cholesterol normal range: 125-200 mg/dl. LDL normal range: <100 mg/dl. HDL normal range ≥40 mg/dl.

Table 3. The relationship between testosterone, LH, FSH, and prolactin hormone levels and stage II and III of the disease.

parameters	Stage II (mean±SD)	Stage III (mean±SD)	Sig ≤0.05*
Testosterone	366.42 (49.81)	381.09 (34.11)	>0.05
LH	6.42 (0.33)	5.19 (0.74)	**<0.05**
FSH	7.41 (0.41)	8.01 (0.32)	**<0.05**
PRL	7.93 (0.14)	8.24 (0.49)	>0.05

serum of the subjects were measured and compared in two groups, As can be seen, there was no significant relationship between the serum levels of these two lipoproteins in the two groups.

In another phase of this study, the level of cytochrome P450 family 11 subfamily A member 1 gene (CYP11A1; NCBI ID 1583) and cytochrome P450 family 17 subfamily A member 1 (CYP17A1; NCBI ID 1586) expression at the mRNA level in two groups was measured by the relative qRT-PCR method. As can be seen in figures 1 and 2, the expression level of these genes in the PCa group was significantly higher than in the BPH group ($p<0.05$). Then, the expression changes of these genes were compared with hormonal, pathological, and biochemical factors of patients in two groups. Pearson's correlation test showed a significant relationship between these genes expression changes and testosterone, LH, FSH, and PRL levels ($p<0.05$); However, no significant relationship was reported between the expression changes of this gene and serum PSA level, prostate volume, and disease stage ($p>0.05$). Among the biochemical factors, only a significant relationship was observed with cholesterol level ($p<0.05$), but no significant relationship was observed with LDL and HDL levels ($p>0.05$).

DISCUSSION

This study was conducted in three phases, which include 1. Prostate cancer-related hormone profiling phase 2.The phase of checking the levels of cholesterol and its derivatives 3. The phase was to investigate the expression of the testosterone biosynthesis pathway genes from the precursor of cholesterol. Among previous prospective investigations examining hormones and prostate cancer, although substantial overall evidence suggests that androgens and pituitary hormones contribute to the etiology of Prostate cancer, no significant associations between hormone levels and prostate cancer risk have been consistently demonstrated. Stattin et al. reported a reduced risk of prostate cancer in individuals with higher circulating total testosterone levels (23), consistent with the

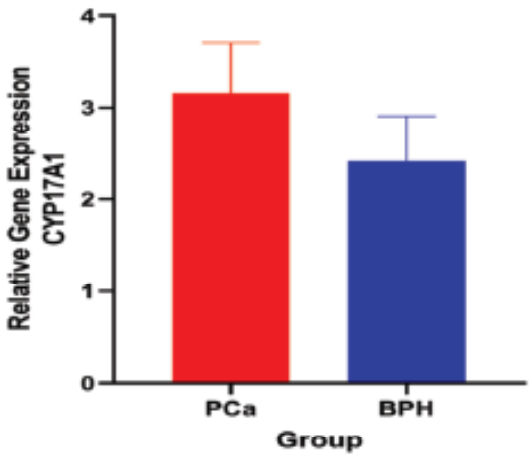

Fig 1. Significant increase in CYP17A1 gene expression in the PCa group compared to the BPH group (p<0.05).

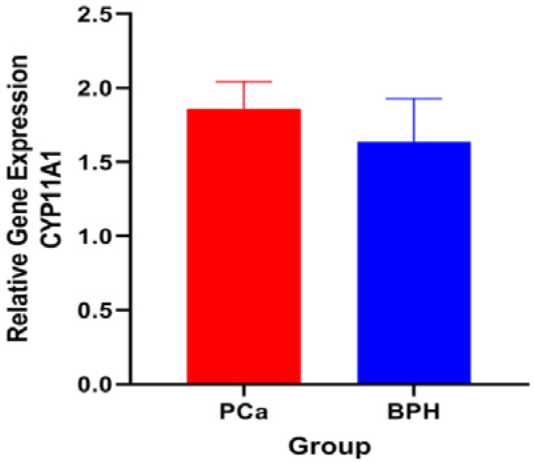

Fig 2. Significant increase in CYP11A1 gene expression in the PCa group compared to the BPH group (p<0.05).

findings of the present study. In rodent tumor models, initiation and progression of prostate cancer have been observed following exposure to exogenous androgens (24). However, the short-term androgen exposure used in animal models may not accurately reflect the chronic, mildly elevated androgen levels typically observed in men.

The results of present study showed that the levels of LH, FSH and PRL hormones were significantly higher in the malignant group than in the benign group; but the level of testosterone in the malignant group was lower than the benign group.

Prostate cancer suppresses testosterone production, likely through local secretion of inhibin or other factors that trigger negative feedback on the hypothalamic–pituitary axis; accordingly, testosterone levels have been reported to increase markedly following radical prostatectomy (25). In addition, because prostate cancer cells offer more binding sites for testosterone than Benign prostatic hyperplasia (BPH) cells, they may function as a reservoir for androgens, thereby reducing circulating testosterone concentrations. Other studies have also shown that low pre-treatment testosterone levels are associated with poorer prognosis (26). Mean testosterone levels decline progressively as the disease advances from organ-confined to metastatic stages (27). Therefore, baseline testosterone levels may be valuable for inclusion alongside other well-established prognostic indicators.

In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells). FSH stimulates testicular growth and enhances the production of an androgen-binding protein by the sertoli cells (28). Some studies have shown, higher LH levels in older men may have an effect on the development of benign prostatic hyperplasia or prostate carcinoma (29). Exposure of cancer cell lines to LH has been linked to upregulation of intratumoral steroidogenesis (30). Enhanced steroidogenic activity is frequently observed in Castration-resistant prostate cancer (CRPC) cells, where it is associated with resistance to androgen deprivation therapy (31). In patients with Prostate cancer, LH levels have been reported to carry prognostic value; however, this observation is inconsistent with findings from other studies, which often show considerable variability. In studies of the hypothalamic–pituitary axis, Harper et al. proposed that low baseline testosterone levels together with elevated LH are indicators of poor prognosis (32), a conclusion also supported by Chen et al. in patients with metastatic prostate cancer, where poor outcomes were found to be independent of tumor grade (33). In the present study, a significant association was observed between disease stage and the levels of LH and FSH.

There may be regulatory interactions between the prostate gland and the pituitary gland. Alterations in the prostate, such as the development of Prostate cancer, can disrupt this interaction and lead to changes in hormone levels, including FSH, LH, testosterone, and free testosterone. In the present study, serum FSH levels were higher in patients with prostate cancer compared to those with Benign prostatic hyperplasia (BPH); however, other similar studies have not identified a significant association between serum FSH levels and the risk of prostate cancer diagnosis. The elevated serum FSH levels observed in cancer patients in this study may be explained by two possible mechanisms: (1) a direct effect of prostate cancer cells on FSH secretion, and (2) the influence of promoter proteins produced by cancer cells that enhance FSH secretion and are associated with reduced testosterone levels.

Limited information is available regarding the role of prolactin (PRL) in Prostate cancer. PRL contributes to

the regulation of genes responsible for the production of PRL-inducible protein in both normal prostate tissue and prostate cancer; transcript levels of this protein have been reported to be significantly higher in carcinoma compared with benign prostate epithelium (33). In the present study, PRL levels were also elevated in the PCa group relative to the Benign prostatic hyperplasia (BPH) group, although this difference did not reach statistical significance.

The cholesterol and its derivatives profile has been of importance in many disease conditions. Its role in BPH and PCa is being examined herein. The results of the present study showed a significant increase in cholesterol levels in the PCa group compared to the BPH group. But there was no correlation between the level of HDL and LDL lipoproteins and prostate cancer.

Cholesterol serves as a fundamental precursor for androgen biosynthesis; therefore, it may contribute to the growth of PCa through its role in steroidogenesis. Raftopoulos et al. demonstrated that cholesterol acts as a critical substrate for de novo steroidogenesis in prostate cells. Their findings indicate that the proliferation of androgen-independent prostate cancer cells can be affected by extracellular lipid levels and the availability of LDL-cholesterol. Moreover, the uptake of extracellular cholesterol via endocytosis of LDL-derived cholesterol followed by its transport and storage as cholesteryl esters within lipid droplets is necessary to sustain prostate cancer cell growth (34). These observations provide further insight into the interplay between extracellular cholesterol, intracellular cholesterol metabolism, and prostate cancer progression, as well as the potential mechanisms linking hypercholesterolemia to more aggressive disease.

Animal model study has shown that high cholesterol levels are significantly related to increased tumor size and increased intracellular testosterone levels. Therefore, it is expected that the expression level of steroids steroidogenic enzymes will increase in cancer cells (35).

In this study, we investigated the expression level of CYP11A1 and CYP17A1, which are enzymes that initiate the conversion of cholesterol to androgens, and the results showed a significant increase in the expression of these two genes compared to the BPH group. This result suggests that cholesterol acts not only as an essential precursor, but also as a pathway agonist, stimulating the upregulation of steroidogenic gene expression. These results are in accord with those of others who demonstrated that proteins responsible for cholesterol regulation are altered during disease progression to increase the pool of available cholesterol, coincident with an increase in androgens to physiologically relevant levels (36). Based on these results, it can be concluded that cholesterol can be used as a therapeutic target in prostate cancer. On the other hand, the results of expressive studies have shown that monitoring steroidogenic genes in patients with PCa may provide useful information for therapy intervention.

In Prostate cancer, tumor cells may produce the androgens testosterone and DHT from adrenal progestagens or dehydroepiandrosterone, provided that CYP17A1, HSD17β3, and HSD3β are expressed within the tumor. Alternatively, when intratumoral androgen production originates from cholesterol, the presence of CYP11A1 is also required. These four enzymes CYP11A1, CYP17A1, HSD3β, and HSD17β3 are recognized as key contributors to the conversion of cholesterol into testosterone. In the present study, increased expression of CYP11A1 and CYP17A1 genes was observed, and in our previous study, elevated expression of HSD3β family genes in prostate cancer was also reported (37).

CONCLUSION

Androgens promote the proliferation of Prostate cancer cells, as well as metastasis and progression to CRPC. In addition to androgenic hormones, pituitary hormones are also involved in the initiation and progression of prostate cancer. LH, FSH, and PRL either independently or in combination with androgens have physiologically important functions in the normal prostate. Their role in the development of Benign prostatic hyperplasia and prostate carcinoma remains an important topic for investigation. In the present study, LH and FSH levels were found to be associated with the occurrence of prostate cancer. Additionally, cholesterol levels, as a precursor for androgen synthesis, were higher in patients with prostate cancer. Consistent with this, the expression levels of genes encoding enzymes involved in androgen biosynthesis from cholesterol were significantly increased. Overall, these findings suggest that monitoring hormonal profiles and cholesterol levels may have an important role in predicting disease progression.

Acknowledgment

The authors would like to thank the Dear officials of Khatam Al-Anbia Hospital

and Department of Molecular Genetics of Ahar Branch Islamic Azad University for supporting this project, also we thank all person contributed to the study. This article is the result of GGV doctoral thesis.

Declarations

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during

the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Funding

Not applicable.

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