Review – Benign Prostatic Hyperplasia

The Potential Role of MicroRNAs as Biomarkers in Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis

Francesco Greco\textsuperscript{a,b,*}, Antonino Inferrera\textsuperscript{c}, Roberto La Rocca\textsuperscript{b}, Michele Navarra\textsuperscript{d}, Marco Casiaro\textsuperscript{e}, Gaetano Grosso\textsuperscript{a}, Sebastiano Gangemi\textsuperscript{e}, Vincenzo Ficarra\textsuperscript{c}, Vincenzo Mirone\textsuperscript{b}

\textsuperscript{a} Department of Urology, Ospedale Pederzoli, Peschiera del Garda (VR), Italy; \textsuperscript{b} Department of Urology, Federico II University, Naples, Italy; \textsuperscript{c} Department of Pathology of Adult and Evolutive Age, University of Messina, Messina, Italy; \textsuperscript{d} Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy; \textsuperscript{e} Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

\section*{Article info}

\textbf{Article history:} Accepted January 9, 2018

\textbf{Associate Editor:} Christian Gratzke

\textbf{Keywords:} miRNA Benign prostatic hyperplasia Prostate cancer Diagnosis Therapy

\section*{Abstract}

\textbf{Context:} Benign prostate hyperplasia (BPH) is one of the most common urologic diseases. However, the molecular and cellular mechanisms involving the stromal and epithelial components of the prostate that lead to BPH remain unclear.

\textbf{Objective:} To review and evaluate the evidence implicating microRNAs (miRNAs) in the pathogenesis of BPH.

\textbf{Evidence acquisition:} A systematic search of the PubMed and Embase databases was performed using the terms "benign prostate hypertrophy and miRNA" or ("benign prostate hypertrophy and microRNAs" or "miRNA" or "miR") on July 31, 2017.

\textbf{Evidence synthesis:} Sixty-four miRNAs from 37 selected articles were ranked according to \(p\) values \((p < 0.05)\). To avoid false positive results, Benjamini-Hochberg correction of \(p\) values was performed. Application of the robust rank aggregation method identified miR-221 as significantly associated with BPH \((p = 0.013)\). The effect size (ES) was calculated for studies with miR-221 data to generate an estimate of the overall ES and its confidence interval. The ES for miR-221 was measured by the standardized mean difference obtained by dividing the difference in the average gene expression between the PCa and BPH groups by a pooled estimate of standard deviation. The random effects model was used to calculate the pooled ES due to the presence of heterogeneity among studies. Publication bias of the seven included studies was assessed by the Funnel plot and Egger’s test and it was detected in the overall analysis of the seven studies \((p < 0.01)\). After the trim and fill procedure, Egger’s test revealed no evidence of publication bias \((p = 0.76)\).

\textbf{Conclusions:} miR-221 has the potential to be used both as a biomarker and novel target in the early diagnosis and therapy of BPH. Technological advances should enable the synthesis of pre-RNA or anti-RNA molecules within carrier vehicles that can be safely delivered into patients. The development of such new pharmacologic therapies should be lastly investigated as possible therapy of one of the most common urologic diseases among elderly men.

\textbf{Patient summary:} miR-221 has the potential to be used both as a biomarker and novel target in the early diagnosis and therapy of benign prostate hyperplasia. The development of new pharmacologic therapies enabling the synthesis of anti-miR-221 should be lastly investigated as a possible therapy of one of the most common urologic diseases among elderly men.

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\* Corresponding author. Martin-Luther University, Clinic of Urology and Renal Transplantation, Ernst-Grube Strasse 40, Halle Saale 06120, Germany. Tel.: +39 3317918535. E-mail address: fgreco@ospedalepederzoli.it (F. Greco).

https://doi.org/10.1016/j.euf.2018.01.008

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1. Introduction

Benign prostatic hypertrophy (BPH) represents one of the most common urologic diseases among elderly men with a major impact on quality of life (QoL) and a substantial economic burden [1,2].

Epidemiologic studies suggest that age, genetic factors, and sexual hormones play major roles as risk factors for BPH, and the only known factors associated with BPH progression are age and prostate volume [3]. More recently, metabolic syndrome, detrusor overactivity, prostatic inflammation, cell-signaling disorders, and neurologic, cardiac, and renal dysfunctions have been hypothesized to contribute to the development of BPH [4]. Despite the well-established role of age, hormonal factors, and genetic predisposition, the molecular and cellular mechanisms involving the stromal and epithelial components of the prostate that lead to BPH remain unclear [5]. In the last few years it has been postulated an influence of microRNAs (miRNAs) in the regulation of urogenital diseases [6]. miRNAs are a group of small RNA molecules of between 19 and 25 nucleotides that can target many genes, as well as genes within the same pathway, making them central regulatory nodes. Deregulated miRNAs can contribute to carcinogenesis as oncomirs, which regulate tumor suppressors, or as tumor suppressor miRNAs, which target oncogenes [7].

In 2011, a systematic review by Catto et al [6] evaluated the association of miRNAs with prostate, kidney, and bladder cancers, concluding that miRNAs are frequently altered in urogenital cancers and as such have the potential to serve as biomarkers or novel therapeutic targets.

Aberrant miRNA expression and specific miRNA signatures have been identified by many groups, demonstrating the involvement of miRNAs in the pathophysiology of prostate cancer (PCa) [8–10].

A recent study identified miR-19a, miR-32, miR-124a, miR-130b, miR-148a, and miR-583 as potential regulators of FLNC, MSRB3, PARVA, PCDH7, PRNP, RAB34, and SORBS1, which correlate with prostate-specific antigen-relapse in PCa patients [10]. Furthermore, several deregulated miRNAs were identified by different groups using different methodologies, offering encouraging results about the prospective use of miRNAs in the diagnosis, prognosis, and therapy of PCa patients [9].

Accumulating evidence supports pathologic links between BPH and PCa in addition to the well-established epidemiologic associations. Anatomic and genetic data also suggest that many PCas are associated with preexisting BPH [10].

The rate of BPH growth is gaining increasing support as both a predictive and prognostic factor for PCa: fast-growing BPH is linked to an increased risk of developing PCa and an increased likelihood that such cancer will be of a high stage or grade [11].

However, knowledge about the association between miRNAs and BPH remains limited, despite the fact that a biomarker for the early diagnosis of BPH could offer the potential to optimize the prevention and treatment of these two commonly coexisting diseases.

The aim of this systematic review was to evaluate the evidence implicating miRNAs in the pathogenesis of BPH.

2. Evidence acquisition

A detailed literature search of the Science Direct and PubMed repositories was performed using the strings “benign prostate hypertrophy and miRNA” or (“benign prostate hypertrophy and microRNAs” or “miRNA” or “mir”) on July 31, 2017.

Relevant papers were selected by two authors (F.G. and S. G.) and all authors fine-tuned and enhanced the list of papers to be included.

Review articles, editorials, commentaries, and letters to the editor were included only if deemed to contain relevant information. Cited references from the selected articles and from review articles retrieved in the search were assessed for significant manuscripts not previously included. Studies published only as an abstract or presented without an abstract, and reports from meetings and studies not published in English were not included in the review. Studies focused on prognosis of PCa, cell line-based studies, and studies with unqualified data were also excluded from the analysis.

The authors selected 37 articles according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (Fig. 1, Table 1) [12].

Results were frequently reported in a list of miRNAs up- or down-regulated with p values as a measure of significance and fold change indicating expression differences between the disease and control groups.

The most frequently used approach to the analysis of miRNAs and the meta-analysis was based on the Robust Rank Aggregation (RRA) method [13,14].

In brief, the method consisted of a comparison of several commonly overlapping miRNAs in a ranked list arising from different studies. Rendering miRNA names comparable across studies was an essential step to achieve a comprehensive meta-analysis.

The selected miRNAs, previously identified in the included studies, were examined by performing a meta-analysis using the Random Effects Model in metfor R-package (R-foundation, Vienna, Austria) [14].

3. Evidence synthesis

The initial search returned a total of 346 manuscripts from the PubMed (n = 68) and Science Direct (n = 278) databases, of which 271 were excluded because of duplication among databases or because they were posters, abstracts, or not Homo sapiens related. Finally, 37 articles including 1561 BPH patients from several countries were subjected to further full-text review (Table 1).

Thirty-five studies examined the expression of miRNAs by quantitative real-time reverse transcription PCR (qRT-PCR) in samples of tissue (n = 20) [8,15–33], urine (n = 2) [34,35], serum (n = 2) [36,37], blood (n = 10) [38–47], or in all three specimens (n = 1) [48]; only two studies performed
high throughput sequencing to compare PCa and BPH using plasma (n = 1) [49] and tissue (n = 1) [50] samples.

The information obtained from multiple independent studies from different platforms was combined in two fundamental steps to perform the meta-analysis.

3.1. miRNA selection

In the first step, 64 miRNAs from selected articles were ranked according to p values (p ≤ 0.05). The ranked lists of miRNAs from each study were combined into a single gene ranking and the RRA method was applied. To avoid false positive results, the Benjamini-Hochberg correction was calculated to adjust p values. After using the RRA method, miR-221 was identified as significantly associated with BPH (p = 0.013).

In 2015, Gunzel et al [27] aimed to identify a miRNA expression signature that could be used to distinguish PCa from BPH. Microarray miRNA profiling of four PCa and four BPH patients revealed that miR-361-3p, miR-133b, and miR-221 were significantly downregulated and miR-203 was upregulated in prostate secretion samples of PCa patients. qRT-PCR results demonstrated that the expression of miR-361-3p was significantly lower in the prostate secretion samples of PCa patients than in those of patients with BPH (p = 0.004). mir-133b (Fig. 2; p < 0.01) and mir-221 (p = 0.03) were also downregulated in PCa compared with BPH. By contrast, the expression levels of mir-203 were significantly upregulated in PCa samples with a p value of 0.0002.

Similarly, Leideinger et al [43] used qRT-PCR to validate five miRNAs that were deregulated between PCa and BPH patients in the microarray analysis. The selected miRNAs included miR-708* and miR-221*, which were downregulated in PCa, and miR-675, miR-1180, and miR-659, which were upregulated in PCa compared with BPH. The significance values by unpaired t test on the Cq values were 0.03 for miR-1180, 0.58 for miR-221*, 0.07 for miR-659, 0.046 for miR-675, and 0.19 for miR-708*. The direction of regulation was confirmed for hsa-miR-708* and hsa-miR-221*. For both miRNAs, the extent of the downregulation was lower by qRT-PCR than by microarray analysis: hsa-miR-708* was downregulated with a fold change of 2.3 and 1.2 and hsa-miR-221* with a fold change of 3.3 and 1.1 by microarray and qRT-PCR analysis, respectively.
<table>
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</table>
3.2. Analysis of the correlation between BPH and miR-221

The effect size (ES) was combined only for studies containing miR-221 data (Table 2) to generate an estimate of the overall ES and its confidence interval. Choi et al [51] described a method to combine ES using a random-effects modeling approach to merge datasets from individual studies of two groups, obtaining an overall estimate of the weighted ES. The ES for miR-221 was measured by the standardized mean difference obtained by dividing the difference in the average gene expression between the PCA and BPH groups by a pooled estimate of standard deviation. The ES was used to measure the magnitude of the treatment effect in each study, and a random effects model was used to incorporate interstudy variability [52].

Figure 2 shows the forest plot of the analysis of miR-221. The random effects model was used to calculate the pooled ES because of the presence of heterogeneity among the studies ($I^2 = 46.2\%$, $p = 0.05$, 95% confidence interval: 0.71–1.61), which could be attributed to the wide-ranging origins of the study cohorts. The studies by Porkka et al [8] and Rauhala et al [31] were based on cohorts of four patients with BPH and nine with PCA; Spahn et al [33] reported only four BPH and eight PCA cases, and Liu et al [21] also had a

![Forest plot](image)

**Table 2** Overall effect size and its confidence interval for studies with miR-221 data.

<table>
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<tr>
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CI = confidence interval; ES = effect size; SE = standard error; Var = variant.

limited cohort size (3 BPH and 5 PCa patients). Higher numbers of patients were reported by Jalava et al. [18] (12 BPH and 42 PCa), Guzel et al. [27] (25 BPH and 23 PCa), and Leidinger et al. [43] (39 BPH and 76 PCa).

To identify studies that may disproportionately influence heterogeneity, Baujat et al. [53] in 2002 proposed a plot to identify studies contributing excessively to heterogeneity and the overall result. The Baujat plot (Fig. 3) identified study 1, Porkka et al. [8], as contributing excessively to heterogeneity and the overall result. A closer look at the characteristics of this study revealed considerable differences in sample size compared with others included in the meta-analysis.

The Funnel plot and Egger’s test were used to assess potential publication bias in the seven included studies (Fig. 4). Publication bias was detected in the overall analysis of the seven studies (p < 0.01). However, after the trim and fill procedure [54], Egger’s test revealed no evidence of publication bias (p = 0.76) as show in Fig. 5. This method adjusts a meta-analysis by imputing “missing” studies to increase funnel plot symmetry. Use of the trim and fill method to adjust the current data provided a reasonable estimate of three missing studies.

4. Conclusions

BPH is a unique condition that is no longer life-threatening; however, its potentially progressive nature has a negative impact on men’s QoL, daily activities, and general health, which may determine the need for lifelong medical therapy or surgery [55]. Moreover, this pathology also presents important social consequences. Its burden extends beyond the sufferer; partners of men with BPH also have significant morbidity associated with their husband’s condition [56].

In addition to the clinical and social implications of the pharmacological and surgical treatment of BPH, the economic costs associated with this disease need to be considered.

In the UK, it is estimated that more than £180 million is spent on BPH treatments each year, with 60% of these costs incurred in secondary care as a direct result of managing BPH complications [57].

Fig. 3 – Baujat plot shows the contribution to heterogeneity for each study represented by Id number.
In the prospective, cross-sectional, observational Trans European Research into the use of Management Policies for Lower Urinary Tract Symptoms suggestive of BPH in Primary Healthcare survey, the mean total 1-yr treatment costs were €858/patient affected by BPH, ranging from €292 in the UK to €1337 in Poland. Medication was by far the most important cost driver, as it accounted for approximately three quarters of the total treatment costs. Surgery costs amounted to 15% and diagnostic testing to 8% of the total cost [58].

All these clinical, social, and economic problems related to the progressive nature of BPH could be resolved by improving our understanding of the molecular and cellular mechanisms involving the stromal and epithelial components of the prostate that lead to BPH.

In recent years, there has been an increasing interest in the codification of miRNAs for the development of therapies for urological diseases.

Because each miRNA can modulate the expression of multiple messengerRNAs (mRNAs) and each mRNA may be targeted by several different miRNAs, it is not surprising that miRNAs are involved in almost all key cellular processes, such as proliferation, differentiation, migration, apoptosis, and stemness maintenance [9].

A growing body of literature has investigated the potential use of miRNAs as biomarkers for cancer diagnosis, prognosis, and therapy [59], including in PCa [60], and the association of miRNA expression levels with clinicopathologic parameters has been demonstrated [50,61,62]. The expression levels of specific miRNAs in clinical prostate tissue samples may be used to detect cancer, predict cancer prognosis, and monitor its evolution, and as markers for therapy selection and response [9].

Accumulating evidence supports that many prostate cancers are associated with preexisting BPH. The rate of BPH growth is gaining increasing support as both a predictive and prognostic factor for PCa: fast-growing BPH is linked with an increased risk of developing PCa and an increased likelihood that such cancer will be of a high stage or grade [11].

Considering the pathologic links between BPH and PCa, we hypothesized that miRNAs expressed in PCa could also be present in patients affected by BPH.
We performed a systematic review of the literature and considered all studies investigating miRNAs in PCa that included patients affected by BPH as a control group.

 Ranked lists of miRNAs produced for each study were aggregated into a single gene ranking and analyzed using the RRA method, which confirmed miR-221 as the only miRNA significantly associated with BPH (p = 0.013). Only seven studies reported data for miR-221. Publication bias in the seven included studies was assessed by Funnel plot and Egger’s test. Publication bias was detected in the overall analysis of seven enrolled studies (p < 0.01). However, after the trim and fill procedure [54], Egger’s test revealed no evidence of publication bias (p = 0.76).

Jalava et al [18] identified five miRNAs regulated by dihydrotestosterone, which plays a beneficial role in the developing prostate [63]: miR-32, miR-148a, miR-99a, miR-21, and miR-221. Four of these, namely miR-32, miR-590-5p, miR-148a, and miR-21 were significantly overexpressed, and three, miR-99a, miR-99b, and miR-221, were significantly underexpressed in castration-resistant PCa.

Liu et al [21] reported that miR-182 expression was significantly upregulated in PCa tissues and in four cell lines compared with BPH, whereas five miRNAs (miR-345, miR-145, miR-221, miR-27b, and miR-378) were downregulated in PCa.

Furthermore, in all studies evaluating the correlation between miRNA-221 and PCa, miRNA-221 was down-regulated in patients with higher Gleason scores, advanced stage tumors, and positive lymph nodes [8,18,21,27,31,33,43].

Recently, Cheinani et al [64] reported mRNA and miRNA transcriptome sequencing of bladder samples from human patients with different urodynamically defined states of bladder outlet obstruction (BOO). From 19 upregulated and 17 downregulated BOO miRNAs, only 221 and 215 mRNA targets, respectively, were present in the BOO mRNA data set.

Although our meta-analysis highlights the potential value of miR-221 as a potential biomarker for BPH, with diagnostic and treatment implications, we cannot forget that BPH is a multifactorial disease, whose pathophysiology has still not been completely elucidated. Another limitation is represented by the lack of studies including as control group patients with PCa or age-matched asymptomatic men with no lower urinary tract symptoms.
In the future, the technology will become less expensive and more prevalent, and it is likely that further advances in our knowledge of the role of miRNAs in human disease will be made. With respect to urologic malignant and benign diseases, miRNAs hold promise as potent biomarkers and novel therapeutic targets. Clinical trials using RNA therapies are awaited, and it is likely that within the next five years these trials will affect the way we treat our patients [6,65].

miRNAs are important modulators of gene expression. They are frequently altered in urologic cancers and they play an important role in the pathogenesis of BPH.

miR-221 has the potential to be used both as a biomarker and novel target in the early diagnosis and therapy of BPH. Technological advances should enable the synthesis of pre-RNA or anti-RNA molecules within carrier vehicles that can be safely delivered into patients. These molecules could be administered topically or systemically to induce generalized cell targeting.

The development of such new pharmacologic therapies should be lastly investigated as possible therapy of one of the most common urologic diseases among elderly men with a major impact on QoL, in an attempt to reduce the great economic burden associated with this disease.

**Author contributions:** Francesco Greco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.  
Study concept and design: Greco, Gangemi.  
Acquisition of data: Greco, Inferrera, La Rocca, Cassignaro.  
Analysis and interpretation of data: Greco, Navarra, Gangemi.  
Drafting of the manuscript: Greco.  
Critical revision of the manuscript for important intellectual content: Ficarra, Mirone.  
Statistical analysis: Greco, Gangemi.  
Obtaining funding: None.  
Administrative, technical, or material support: None.  
Supervision: Grosso, Mirone.  
Other: None.

**Financial disclosures:** Francesco Greco certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

**References**


EUF-440; No. of Pages 11

AR T I C L E  I N  P R E S S

EUROPEAN UROLOGY FOCUS XXX (2018) XXX–XXX

11


