Reports of Practical Oncology and Radiotherapy 25 (2020) 163–167

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Metformin and statins: a possible role in high-risk prostate cancer

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ARTICLE INFO

Article history:
Received 15 September 2019
Accepted 30 December 2019
Available online 9 January 2020

Keywords:
Metformin
Statins
Radiotherapy
Prostate cancer
Survival

ABSTRACT

Aim and background: There is increasing evidence that statins and oral anti-diabetic drugs, such as metformin, can have a favorable role in advanced prostate cancer treatment.

Metformin has been shown to inhibit proliferation of tumor cells in vitro and statins inhibit carcinogenesis by suppressing angiogenesis/invasion mechanisms. However, clinical evidence on the protective effect of these drugs is still weak.

The purpose of this study is to analyze if these drugs have an impact on Biochemical-Failure-Free-Survival (BFFS) and on Distant-Failure-Free-Survival (DFFS) in localized high-risk prostate cancer.

Material and Methods: From 2002–2016, 447 patients with histologically confirmed high-risk prostate cancer were retrospectively evaluated. All patients received radiotherapy and androgen deprivation therapy. Biochemical recurrence was determined by the Phoenix criteria and metastatic patients were defined by the presence of radiological metastasis. Survival analysis was performed using the Kaplan-Meier method.

Results: 175 patients were treated with statins (65.3 % with a dose $\leq$ 20 mg/day) and 70 with metformin (75.7 % with a dose $\leq$ 1700 mg/day). Median follow-up was 88 months (1–194) with no differences in BFFS and DFFS between metformin and non-metformin patients (77.4 % versus 80 %, p = 0.91 and 89.4 % versus 88.7 %, p = 0.56, respectively). We did not find a statistical difference in BFFS and DFFS in patients taking higher doses of those drugs.

Conclusion: Metformin and statins were not associated with BFFS or DFFS improvement in our analysis. However, the small number of patients treated with these drugs limits the reliability of the results and prospective studies are needed.

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1. Aim and background

There is increasing evidence that statins and oral anti-diabetic drugs, such as metformin, can have a favorable role in Prostate Cancer (PCa) treatment. Clinical studies have demonstrated that diabetic patients on metformin had lower cancer incidence and a better cancer-specific survival in comparison with diabetics taking other anti-diabetic drugs.[1] Moreover, retrospective studies in PCa patients showed that metformin treatment is associated with a lower incidence and recurrence of prostate cancer in diabetic patients.[2] These outcomes are congruent with in vivo studies proving that metformin combined with bicalutamide can reduce PCa growth in murine models.[3] Moreover, in vitro studies have demonstrated the anti-proliferative effect of metformin on PCa cells growth.[4,5] Metformin seems to have anti-cancer effects through two different mechanisms (Fig. 1): in a direct way, acting on the tumor, and indirectly by lowering insulin levels.[6]

The direct effect is insulin-independent and is induced by the inhibition of the Mitochondrial Complex I and the following activation of the 5′ Adenosine Monophosphate-Activated Protein Kinase (AMPK). Activation of AMPK results in the inhibition of Mammalian Target of Rapamycin (mTOR) which is a key mediator of the phosphatidylinositol-3-kinase/protein kinase B/Akt (PI3K/PKB/Akt) pathway. This is crucial, since several important signaling pathways, including those previously mentioned, are frequently altered in human tumors.[7] Consequently, mTOR inhibition decreases protein synthesis and tumor cells proliferation. Furthermore, AMPK activation may have more effects on other

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https://doi.org/10.1016/j.rpor.2019.12.027
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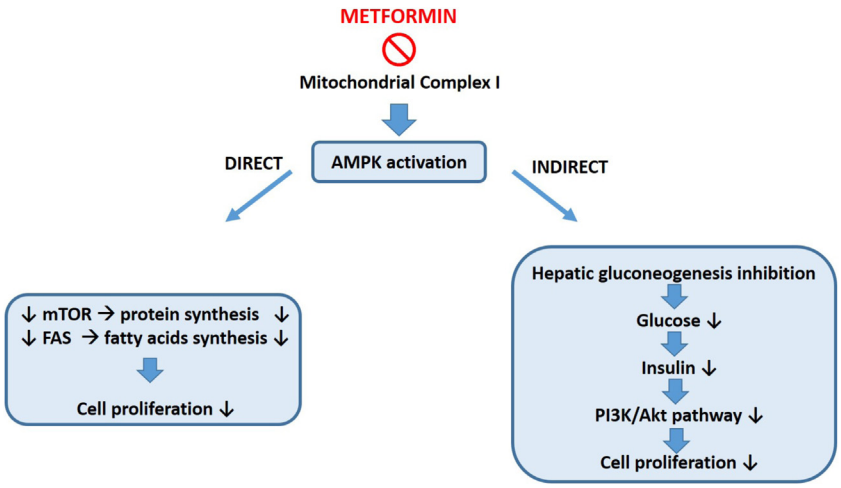

Fig. 1. Direct and indirect anti-cancer effects of metformin.

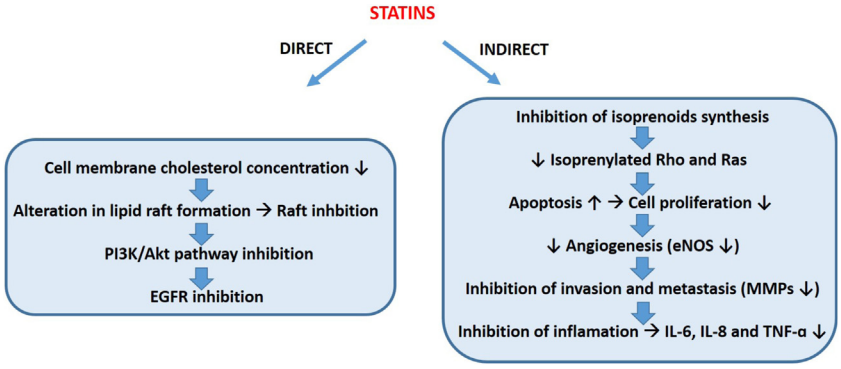

Fig. 2. Direct and indirect anti-cancer effects of statins.

metabolic pathways by blocking Fatty Acid Synthase (FAS). This inhibition causes the reduction of fatty acids which are critical in PCa metabolism.[8] Metformin also exerts an indirect effect, which is insulin-dependent, and it is probably related to the inhibition of hepatic gluconeogenesis via AMPK. In fact, AMPK activation interrupts gluconeogenesis genes transcription and induces glucose uptake in muscles, diminishing glucose and insulin levels. Insulin reduction leads to a down-regulation of the PI3K/Akt pathway, which participates in tumor cells proliferation and in mechanisms of migration and stromal invasion.[9] As for as statins are concerned, they are widely employed to decrease blood cholesterol levels. Preclinical studies show that cholesterol may promote prostate carcinogenesis in rats, while statins seem to have a protective effect in PCa. Those drugs might inhibit carcinogenesis by inducing apoptosis and preventing mechanisms of angiogenesis and invasion (Fig. 2).

This happens with a direct mechanism, by lowering cholesterol levels, and also with pleiotropic cholesterol-independent effects.[10]

Testosterone synthesis starts from cholesterol and progestin precursors through a steroid pathway involving multiple enzymes. The initial step of steroidogenesis involves cholesterol transportation from the outer to the inner mitochondrial membrane. Cholesterol is converted to pregnenolone by the enzyme P450 side chain cleavage (P450scc) and exported to the endoplasmic reticulum where it is transformed into testosterone through the subsequent action of different enzymes (Fig. 3). Thus, statins by lowering cholesterol levels may also decrease the novo testosterone synthesis in PCa cells and prevent the evolution to metastatic disease.[11]

The cholesterol located in cell membrane seems to activate anti-apoptotic PI3K/Akt and EGFR signalling pathways in PCa. Therefore, statins reduce membrane cholesterol concentration, which alters lipid raft formation and its integrity and, this way, they could inhibit prostate cell proliferation.

In fact, lipid rafts contain androgen receptors (ARs) that regulate intracellular signaling pathways and spread androgen-dependent signals to the PI3K/Akt pathway.[12]

Moreover, lipid rafts can activate Epidermal Growth Factor Receptor (EGFR) mediated signaling, which is often over-expressed in PCa and it has been shown to be associated with a more aggressive disease and a significantly increased risk of biochemical failure. EGFR contains a lot of domains rich in cholesterol; thus, statins, by altering raft formation, can inhibit EGFR/Akt and EGFR/ERK pathways and promote apoptotic cell death via down-regulation mechanisms.[13]

Statins also exert pleiotropic effects, because of isoprenoids synthesis inhibition, which is crucial for proteins activation through the isoprenylation mechanism.

Rho and Ras proteins control the signal transduction of different membrane receptors with tyrosine kinase activity and their activation, via isoprenylation, determine a downstream regulation, which endorses cell survival.[14]

Statins, through the inhibition of Rho and Ras isoprenylation, promote apoptosis and also diminish angiogenesis, via eNOS down-regulation, and inhibit invasion and metastasis mechanisms by reducing Matrix Metallo-Proteinases expression (MMPs), which damages Extra-Cellular Matrix (ECM).[15]

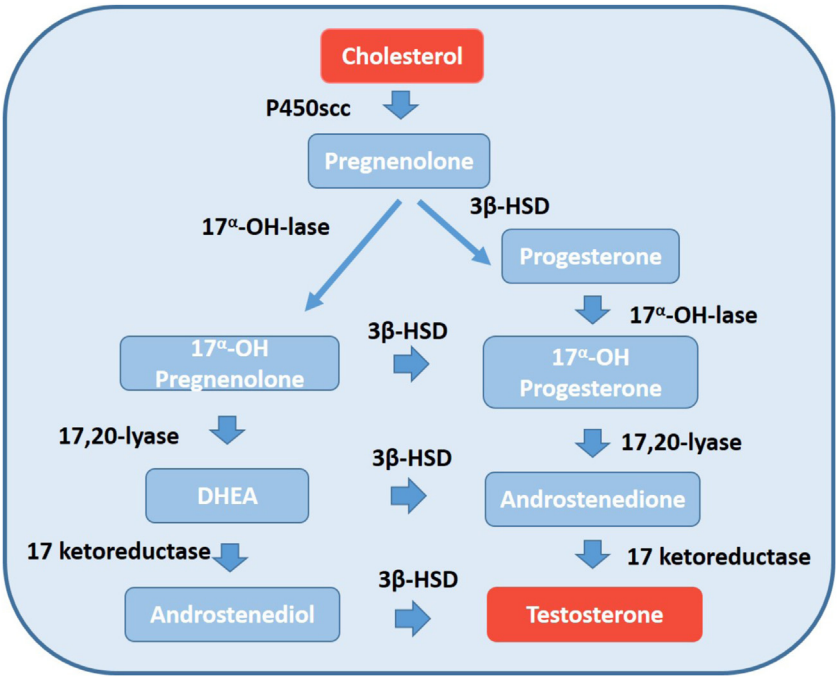

Fig. 3. Steroid biosynthetic pathway involving cholesterol.

However, statins show pleiotropic effects in vitro at relatively high concentrations which are not normally prescribed in patients treated at therapeutic doses.[11] Moreover, statins have been shown to cause both anti-angiogenic and pro-angiogenic effects according to the dose: high doses seem to inhibit angiogenesis (through Rho inhibition), while low doses exert the opposite effect.[16]

Finally, statins reduce systemic inflammation and consequently intratumoral inflammation, which is associated with PCa progression, with the inhibition of pro-inflammatory molecules production, such as IL-6, IL-8 and TNF-α.[17]

Notwithstanding, clinical evidence on statin protective effects in PCa is still weak and observational studies or meta-analyses have not found any influence on prostate cancer risk. Future clinical trials are expected to elucidate statins role in prostate carcinogenesis.[18,19] The purpose of this study is to analyze if metformin and statins have an impact on Biochemical-Failure-Free-Survival (BFFS) and on Distant-Failure-Free-Survival (DFFS) in localized high-risk prostate cancer patients.

2. Material and methods

From 2002–2016, 447 patients with histologically confirmed high-risk prostate cancer defined by the National Comprehensive Cancer Network (NCCN) risk group were retrospectively evaluated. All patients assumed Androgen Deprivation Therapy (ADT) for a minimum of 2 years and received treatment with radiotherapy according to our institution protocol (72–76 Gy).

Biochemical recurrence was determined by the Phoenix criteria defined as a PSA rise of 2 ng/mL or more above the nadir PSA and metastatic patients were defined by the presence of radiological documented metastasis (CT scan, MRI, Choline-PET or bone scintigraphy) in the nodes, bones, or visceral disease according to RECIST 1.0 criteria. Association with BFFS and DFFS was analyzed using the Kaplan and Meier method.

Table 1
Patients characteristics.

Patients characteristics (N = 447)
Median age (years) 70 (46–83)
Median PSA (ng/ml) 34 (3.8–766)
Gleason score
≤ 7 41.5 % (N = 186)
≥ 8 58 % (N = 258)
Pathological tumor size
T1-T2 74.7 % (N = 334)
T3-T4 25.2 % (N = 113)
Pathological nodes
N0 99 % (N = 441)
Statins users 39 % (N = 175)
Dose ≤ 20 mg/day 65.3 % (N = 115)
Metformin users 15.6 % (N = 70)
Dose ≤ 1700 mg/day 75.7 % (N = 53)

3. Results

Patients' characteristics are shown in Table 1. We studied 447 patients with a median age of 70 years (46–83) and median PSA at diagnosis of 34 ng/ml (3.8–766). Of the patients included in this study, 39 % (N = 175) were treated with statins (65.3 % with a dose ≤ 20 mg/day) and 15.6 % (N = 70) were treated with metformin (75.7 % with a dose ≤ 1700 mg/day).

With a median follow-up of 88 months (1–194), no significant statistical differences were found in BFFS and DFFS among metformin versus non-metformin patients (77.4 % versus 80 %, p = 0.91 and 89.4 % versus 88.7 %, p = 0.56, respectively), as shown in Fig. 4. Regarding the types of statin, the most used were Simvastatin in 19 % of patients (N = 85) and Atorvastatin in 18.6 % (N = 83).

BFFS and DFFS in patients receiving ≤ 1700 mg/day versus ≥ 1700 mg/day of metformin was 78.2 % versus 56 % (p = 0.10) and 93.3 % versus 71 % (p = 0.12).

In statins patients versus non-statins patients, BFFS at 88 months was 78 % versus 81.2 % (p = 0.25) and DFFS was 90 % versus

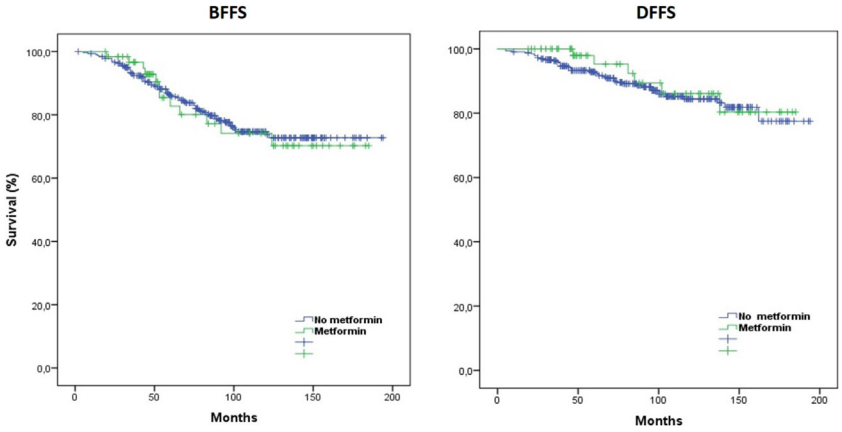

Fig. 4. BFFS and DFFS survival in patients on metformin versus non-metformin.

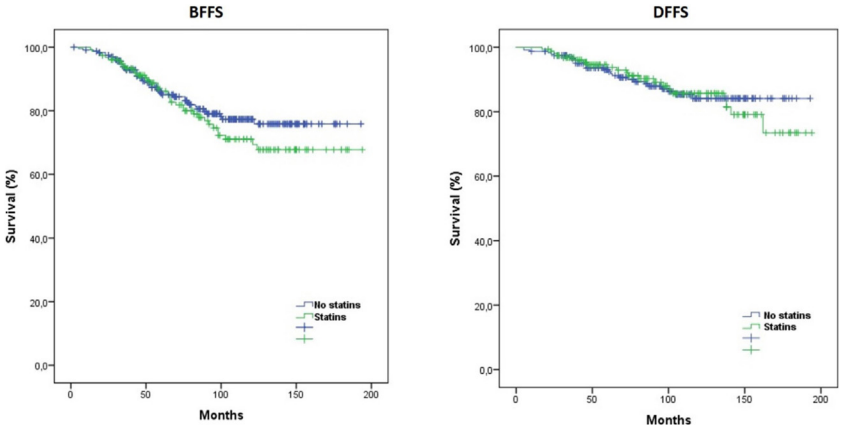

Fig. 5. BFFS and DFFS survival in patients on statins versus non-statins.

88 % (p = 0.79). Moreover, BFFS and DFFS in patients receiving ≤ 20 mg/day versus ≥ 20 mg/day of statins was 74.3 % versus 81.7 % (p = 0.29) and 90 % versus 90.3 % (p = 0.82), respectively (Fig. 5).

Overall Survival (OS) considering all patients included in this study, was 83.2 % at 88 months and Disease Specific Survival (DSS) was 97.4 %. We did not find any statistical difference in OS in patients on metformin compared to non-metformin (90.2 % versus 90.5 %; p = 0.92) but OS in patients taking statins was statistically better compared to patients not treated with this drug: 87 % versus 80 % at 88 months (p = 0.001). However, no difference was observed in DSS in patients on statins versus non-statins (98 % and 97.6 %, respectively; p = 1.14), nor in the metformin versus non-metformin group (97.1 % and 97.9 %; p = 0.6).

We also analyzed the concomitant use of statins and metformin and we did not find an improvement in BFFS or DFFS compared to patients taking only one of those drugs: 90.2 % versus 89.3 % (p = 0.7) and 94 % versus 92.5 % (p = 0.5).

The consumption of metformin was associated with an increased risk of acute genitourinary toxicity (OR 1.4; 95 % CI, 0.3-0.9; p = 0.018) but there was no association with an increased risk of chronic genitourinary toxicity (OR 1.0; CI 95 %, 0.5–1.8; p = 0.9), neither with acute (OR 1.0; CI 95 %, 0.5–1.6; p = 0.8) nor chronic gastrointestinal toxicity (OR 1.1; CI 95 %, 0.3–2.3; p = 0.8).

Likewise, statins use was associated with a higher risk of acute genitourinary toxicity (OR 1.2, 95 % CI: 0.4–1; p = 0.06), with no difference regarding chronic genitourinary toxicity (OR 1.0; 95 % CI, 0.6–1.5; p = 0.9) and acute (OR 1.1; 95 % CI, 0.7–1.8; p = 0.4) or chronic gastrointestinal toxicity (OR 1.5; 95 % CI, 0.7–2.9; p = 0.2).

4. Discussion

Our results do not support the hypothesis that statins or metformin, regardless of the therapeutic dose, can reduce the risk of PCa recurrence among patients treated with ADT and radiotherapy. These findings are congruent with previous results observed in different meta-analysis which have shown that the use of statins does not seem to reduce the risk of PCa,[18,20] nor the risk of biochemical recurrence in men treated with radical prostatectomy or radiotherapy.[21,22] However, in recent meta-analysis, patients on statins had a lower risk of prostate cancer-specific mortality (HR = 0.68, 95 % CI: 0.56–0.80) and a trend towards increasing the biochemical recurrence free survival rate.[23] Overall, different meta-analysis showed heterogeneous results regarding statins use and PCa outcomes.

As far as metformin is concerned, different meta-analysis could not find any association between metformin use and all-cause mortality or PCa recurrence in diabetic patients and no association with prostate cancer-specific mortality.[24,25] Although we found a better OS in men taking statins, this finding is probably a confounding effect because of the protective effect against cardiovascular diseases, which might imply that statins have a beneficial effect. Nonetheless, this is not the case.

In our study, the majority of patients took metformin and statins at low doses and we found no difference in tumor control compared with patients taking higher doses. Some studies found that statins had anticancer properties but in vitro studies showed that the protective effect appears with higher doses than the therapeutic ones and whether high statin concentration is required

in vivo is still unknown.[26] We also observed that statins and metformin use had a neutral effect on DSS. Those results are in contrast with the findings of a previous Chinese meta-analysis of 22 studies that found a lower prostate cancer-specific mortality and a trend towards a better DFFS risk in statins users.[23] Currently, there are on-going phase I/II clinical trials to further clarify the possible role of statins and metformin in localized PCa.

For example, The METAL trial is a randomized, placebo-controlled, double-blind study exploring the possible metformin effect in patients recently diagnosed with localized PCa. All patients will undergo radical prostatectomy and randomized 1:1 to receive, for 4 weeks, 2 g of metformin per day or placebo before the surgery. The primary endpoint will measure the expression level of the Fatty Acid Synthase/AMPK pathway before and after surgery in the two arms, by analyzing the diagnostic biopsy and prostatectomy specimens.

Secondary endpoints is to find the difference in expression levels proliferation markers, such as ki67 and TUNEL.[27]

Metformin and statins use was relatively safe and we only observed a higher risk of acute genitourinary toxicity in metformin users. The combination with radiotherapy seems to be a reliable treatment with similar toxicity compared to radiotherapy alone.

This retrospective study has some limitations. First, the small number of patients taking metformin and statins limits the statistical power of the study. Secondly, patients were treated with different types of statins and commencement dates were different regarding radiotherapy treatment (some patients started using statins or metformin before radiotherapy, during treatment or after radiotherapy), which might contribute to the heterogeneity of this work.

5. Conclusions

In our study the use of metformin and statins was not associated with an improvement of BFFS and DFFS, regardless of the dosage. Prospective studies and phase III clinical trials are needed to clarify confounding factors such as metformin and statins dosage, treatment timing and patient compliance.

Finally, results of on-going clinical trials will be crucial to better define the clinical use of metformin and statins in PCa and the possible synergism with radiotherapy and ADT.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval retrospective studies: No needed

Informed consent

There is no consent for this work

Financial disclosure statement

There are no financial conflicts of interest to disclose.

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