Clin Thyroidol 2013;25:264–266.

Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION
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Metformin Inhibits Thyrocyte Growth and Increases Complete Responses in Differentiated Thyroid Cancer in Patients with Diabetes

Artak Labadzhyan

Klubo-Gwiezdzinska J, Costello J Jr, Patel A, Bauer A, Jensen K, Mete M, Burman KD, Wartofsky L, Vasko V. Treatment with metformin is associated with higher remission rate in diabetic patients with thyroid cancer. J Clin Endocrinol Metab 2013;98:3269-79. Epub May 24, 2013.

SUMMARY

Background

Obesity and type 2 diabetes have both been linked to an increased risk for some types of cancer. Metformin has been shown to have antineoplastic effects in various cancers, and there are some encouraging data for its role in neoadjuvant and adjuvant therapy. In a prior study, these authors found that metformin decreased the growth of medullary thyroid cancer cells and down-regulated p70S6K and MAPK kinase/ERK signaling (1).

Methods

Medical records were evaluated retrospectively for the efficacy of thyroid cancer therapy in 240 patients who were followed for a mean (±SD) of 6.9±4.8 years. Inclusion criteria included a diagnosis of differentiated thyroid cancer (DTC), follow-up data after surgery and radioactive iodine (RAI) ablation, and a diagnosis of type 2 diabetes mellitus before the diagnosis of DTC. Patients were categorized into three groups: group 1 (n = 34) had been treated with metformin, group 2 (n = 21) had not received metformin therapy; and group 3 (n = 185) were control patients with DTC who had no history of diabetes or metformin use. The dose of metformin ranged from 500 mg to >2000 mg daily, with 21 of 34 patients receiving 1000 to 1500 mg/day. The mean duration of metformin treatment was 4.4±3 years. Complete response was defined as undetectable Tg levels (both suppressed and stimulated) and no evidence of disease on imaging studies. Progression-free survival (PFS) was assessed from the day of the last dose of RAI therapy until the last imaging study performed during the follow-up period. A multivariate logistic-regression model was used to compare treatment efficacy, and a Cox proportional-hazard models was used to assess significant factors affecting PFS.

The authors extended their previous studies with metformin to human follicular and papillary thyroid cancer cell lines, assessing proliferation, viability, and migration activity. Responses of cell signaling markers like phospho/total p70S6K, phospho pS6, phospho/total AKT, phospho/total ERK, phospho/total AMPK, poly polymerase (PARP), cyclin D1 to H2O2 stress were measured by Western blotting. Some human thyroid cancer samples were also immunostained for p-AMPK and phospho p70S6K.

RESULTS

The patients in the diabetes groups were similar in age, sex, mean glycated hemoglobin, mean body-mass index, insulin use, duration of insulin use, and use of other antidiabetes medications. The initial tumor size was significantly smaller in the patients with diabetes who received metformin; in contrast, the total amount of RAI given was higher in patients with diabetes who were not taking metformin and their mean TSH levels during follow-up was higher. The complete response (CR) rate was significantly lower in the patient with diabetes who were not taking metformin than in the controls or the patient with diabetes who were taking metformin; the duration of metformin treatment

continued on next page

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Artak Labadzhyan

was not associated with complete response. Lack of treatment with metformin, presence of gross extrathyroidal extension, and distant metastases were significantly associated with lower CR rates (odds ratios, 0.03, 0.092, and 0.005, respectively). Age at diagnosis of cancer, lack of treatment with metformin, presence of lymph-node metastases, and presence of distant metastases were significantly associated with a risk for shorter progression-free survival (hazard ratios, 1.059, 9.218, 7.614, and 17.359, respectively).

Exposure to higher concentrations of metformin (5 mM) and to longer treatment times (3 days) made thyroid cancer cells grow somewhat more slowly, but metformin had no effect on cell migration. Metformin increased p-AMPK while inhibiting cyclin D and downstream targets of the mammalian target of rapamycin (mTOR) such as phospho p70S6K. Pretreating cells with 1 mM metformin increased their sensitivity to 0.1 to 0.5 mM H2O2, decreasing prosurvival signaling via pERK, while activating AMPK. Metformin did not affect the expression of sodium–iodide symporter. Immunostaining was positive for phospho p70S6K in cancer tissue from three of the six patients with diabetes who were not taking metformin, but it was negative in three samples from patients taking metformin.

CONCLUSIONS

In patients with diabetes who have differentiated thyroid cancer, metformin treatment is an independent factor for an increased likelihood for complete response, restoring it to the level of normal controls, and was also associated with longer progression-free survival. A possible molecular mechanism may involve metformin's action via the adenosine monophosphate-activated protein kinase (AMPK) pathway to inhibit cell growth, down-regulating cyclin D1 expression and downstream targets of mTOR.

ANALYSIS AND COMMENTARY

This study combines clinical and in vitro analyses to demonstrate a possible role for metformin in the treatment of DTC. The clinical data raise the possibility that metformin treatment affects tumor size. Although it could simply be due to chance, the 34 patients with diabetes who had been taking metformin had significantly smaller tumors, as compared to the 21 patients with diabetes who had not taken metformin or to the 128 controls (1.37 cm vs. 2.44 cm vs. 2.39 cm, respectively). It is somewhat worrisome that after RAI treatment, the mean TSH in the patients with diabetes who had not been taking metformin (0.65±0.79) remained at a significantly higher level than the mean TSH in patients with diabetes who were taking metformin (0.36±0.30) or in the controls (0.34±0.46). There is much controversy concerning the effects of metformin on TSH levels, and results may be influenced by multiple confounding factors, such as weight, smoking, and goiter.

A small prospective study has been performed on patients with insulin resistance as well as small nodules that were shown to be benign by FNAB: it found that 6 months of metformin resulted in a significant reduction in nodule size (2). Obviously, a prospective study with a larger size will be necessary to establish the association between metformin treatment and DTC response and survival, although this may be difficult to achieve. Nonetheless, this study suggests that metformin promotes pathways that lead to down-regulation of prosurvival signaling and to up-regulation of destructive signaling, which may make the cancer cells more amenable to the oxidative stress produced by cancer treatment. The results in the in vitro study underscore the importance that the AMPK-dependent pathways play. The modulation of AMPK by metformin may be the key step in determining the efficacy of metformin in the treatment of thyroid cancer.

continued on next page

Metformin Inhibits Thyrocyte Growth and Increases Complete Responses in Differentiated Thyroid Cancer in Patients with Diabetes

Artak Labadzhyan

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