Metformin Decreases Serum Thyroglobulin Concentration in Nonmedullary Thyroid Carcinoma

Celina Caetano,1 Paola Tabaro Pico,2 Charan Singh,2 Beatriz Tendler,1 Diana M. Malchoff,1 and Carl D. Malchoff1,3

1Neag Comprehensive Cancer Center, University of Connecticut Health Center, 263 Farmington Avenue, Farifield, CT 06030, USA
2Department of Radiology, University of Connecticut Health Center, 263 Farmington Avenue, Farifield, CT 06030, USA

Correspondence: Carl D. Malchoff, MD, PhD, 263 Farmington Avenue, Farifield, CT 06030, USA. Email: Malchoff@uchc.edu

Abstract

Context: The conventional treatment of nonmedullary thyroid carcinoma (NMTC) includes surgical resection, thyrotropin (TSH) suppression, and 131-iodine. Some patients develop persistent/recurrent metastatic disease requiring expensive alternative therapies, such as external radiation and multikinase inhibitors, which may have clinically significant side effects. Recent in vitro studies, in vivo studies in animals, and association studies in humans suggest that metformin, an inexpensive medication with a modest side effect profile, may help prevent or treat NMTC. No interventional trials analyzing the effect of metformin have been performed in humans.

Objective: We hypothesize that metformin administration will decrease serum thyroglobulin concentration (Tg), a surrogate marker for NMTC burden.

Methods: This retrospective institutional review board–approved study included 10 patients with persistent/recurrent NMTC who had exhausted conventional therapies including total thyroidectomy and 131-iodine. Five had detectable disease on computed tomography imaging. All had biochemical evidence of NMTC with Tg > 2.0 ng/mL with nondetectable serum thyroglobulin antibody concentrations. Five elected to have metformin treatment at doses varying from 500 to 2000 mg/day for 2 to 5 months. The remaining 5 served as untreated controls. Statistical significance was determined by the Mann–Whitney test.

Results: Tg decreased (mean decrease = 21.7 ± 8.4%) in all 5 patients receiving metformin and increased (mean increase = 16.6 ± 12.1%) in all 5 controls (P < .01). TSH did not change significantly in either group.

Conclusion: In summary, metformin caused a TSH-independent Tg decrease in patients with persistent/recurrent NMTC. More extensive studies are required to determine if metformin slows NMTC progression

Key Words: thyroid cancer, metformin, thyroglobulin, mTOR, AMPK

Abbreviations: CT, computed tomography; PTC, papillary thyroid cancer; Tg, thyroglobulin concentration; TSH, thyrotropin; NMTC, nonmedullary thyroid carcinoma.

The incidence of thyroid cancer has been increasing significantly over the past years [1]. Over 90% of such cases are nonmedullary, indicating an origin from the thyroid epithelial cells [2, 3]. Most patients with nonmedullary thyroid carcinoma (NMTC) are successfully treated by a combination of surgical resection, thyrotropin (TSH) suppression with thyroid hormone, and, when necessary, 131-iodine. However, between 7% and 25% of patients escape conventional therapies, develop recurrent/persistent disease, and are at greater risk for NMTC progression and death [4–6]. Alternate therapies such as external radiation and multikinase inhibitors are expensive and have a clinically significant side effect profile [7]. Therapies with a more benign side effect profile would provide these patients with a beneficial option.

Metformin may have beneficial effects in epithelial cell malignancies. This inexpensive biguanide has a minimal and reversible adverse side effect profile and is FDA approved for first-line management of type 2 diabetes mellitus. Retrospective association studies in humans have demonstrated that diabetic patients treated with metformin have a higher NMTC remission rate and a reduced NMTC risk compared with patients with diabetes not receiving metformin [8, 9]. Metformin may have antitumorigenic properties, since in vitro and in vivo animal studies demonstrate that metformin or phenformin, another biguanide, inhibit the growth of not only thyroid cancer but other epithelial cell–derived cancers such as breast, colon, and melanoma [10–12].

We reasoned that a beneficial effect of metformin on NMTC would be reflected in a decreased serum thyroglobulin concentration (Tg), a circulating marker for NMTC tumor burden. No interventional studies have reported the effect of metformin on NMTC. In this study, we use an interventional approach to test the hypothesis that metformin will decrease serum Tg in patients with persistent/recurrent NMTC.
Material and Methods

Study Design

We retrospectively analyzed the effect of metformin administration on Tg and TSH in patients with recurrent/persistent NMTC, and, when available, computed tomography (CT) images of NMTC. The primary endpoint was Tg. The secondary endpoint was time to progression as determined by CT evidence of NMTC. TSH (a NMTC growth stimulator) measurements were made to verify that the changes in Tg were not due to confounding changes in TSH. Measurements of Tg, TSH, weight, and CT scans were performed at the initiation of therapy and after 2 to 6 months of therapy. The metformin dose was at the discretion of the treating physician.

The University of Connecticut Health Center institutional review board approved this Health Insurance Portability and Accountability Act in place of HIPAA - compliant study.

Patients

All patients were informed that there was biologic plausibility that they may benefit from metformin therapy, but that metformin was not FDA approved for the treatment of NMTC and that there were no published trials investigating the effect of metformin intervention on NMTC in humans. Furthermore, they were informed of the potential complications of metformin including the financial expense and the side effects of nausea, vomiting, diarrhea, and life-threatening lactic acidosis. Each participating patient was informed of her/his results and had the opportunity to discontinue the metformin at any time.

Patients were over 18 years old and had follicular or papillary persistent/recurrent NMTC. All had Tg > 2.0 ng/mL and no circulating thyroglobulin antibodies. The NMTC was not amenable to the usual treatment with 131-radioiodine therapy because the NMTC was no longer iodine avid, the patient had reached the maximal safe cumulative 131-iodine dose, or because the patient refused further 131-iodine therapy. Patient 8 had received head and neck external radiation. In the 12 months prior to the study, no patient received external radiation or 131-iodine therapy. The patients had elected not to be treated with multikinase inhibitors because their NMTC was progressing very slowly, their NMTC did not involve any critical structures, or because they preferred to avoid the side effects of multikinase inhibitors. To minimize the potential of lactic acidosis, patients offered metformin treatment had a serum creatinine concentration of <1.4 mg/dayL for men and <1.3 mg/dayL for women.

Metformin Treatment

The treatment group patients received metformin at doses of 500 to 2000 mg/day and continued this therapy for at least 2 months. One patient (Patient 4) had diabetes and had been on 1000 mg/day metformin for over 2 years prior to entering the study and the metformin dose was increased to 2000 mg/day at the onset of the study. None of the other patients had ever received metformin. Three control patients elected against metformin because of fear of side effects. Two control patients were >80 years old and elected not to be treated because of concerns of side effects and the FDA black box warning for the use of metformin in individuals older than 80 years. One patient (Patient 1) agreed to repeated measures of Tg and TSH over a 35-month period during which metformin was periodically discontinued for 6 days prior to and 2 days following CT imaging to evaluate disease progression. Tg and TSH were measured immediately prior to discontinuing metformin, 5 to 7 days later immediately prior to the CT imaging, and 7 to 9 days later after having restarted the metformin 48 hours after the CT with contrast.

Biochemical Analysis

Tg, TSH, and serum concentration of thyroglobulin antibodies were measured in commercial assays. Some patients used different laboratories, but each patient always used the same laboratory using the same assay. Tg was measured in 9 patients using the Beckman Coulter Access DxI chemiluminescent method (catalog # IM1063, RRID:AB_131588) and in 1 patient (Patient 1) using the Siemens (DPC) chemiluminescent method (catalog # L2KGT2, RRID:AB_2756379). This patient (Patient 1) underwent long-term follow-up and the laboratory changed to the Beckman Coulter Access DxI chemiluminescent method. The interassay coefficient of variation in the Beckman Coulter Access DxI chemiluminescent assay was 7% at 11.4 ng/mL, 43.4 ng/mL, and 81.2 ng/mL, similar in the Siemens (DPC) chemiluminescent assay. The level of detection in both assays was 0.1 ng/mL. TSH was measured using Abbott laboratories reagents (catalog # 7K62, RRID:AB_2883972).

Determination of Progression-free Survival

Analysis of disease progression in 3 of the 5 patients on metformin took place at the University of Connecticut Health Center (Farmington, CT). CT chest radiographs with intravenous contrast were analyzed prior to metformin administration and during treatment. Radiologists (authors P.T.P. and C.S.) retrospectively measured metastatic disease progression in patients on metformin. Progression-free survival was determined using RECIST 1.1 criteria and taken to be the time of the CT scan prior to measurable progression.

Statistical Analysis

Percent change in Tg, as opposed to absolute value of Tg, was chosen for expression of the data graphically, since the range of baseline Tg differed by over 100-fold. However, for statistical analysis, the absolute change of Tg of the treated group was compared with that of the control group using the Mann–Whitney test. A nonparametric test was chosen for this analysis, since the variances of the 2 groups were not equal. Statistical significance was accepted for P ≤ .05. The paired Student’s t-test was used to determine whether the changes in TSH and weight following the initiation of metformin were statistically significant.

Results

All 10 patients meeting the qualifying criteria were included in this analysis. Their clinical characteristics, NMTC type, baseline Tg, sites of metastatic disease, CT imaging results, and metformin doses are summarized in Table 1. Two patients (1 and 4) had a significant family history of papillary thyroid cancer (PTC). Five patients had PTC, 1 had tall cell variant of PTC, 3 had follicular thyroid cancer, and 1 had Hurthle cell thyroid cancer. Five (1, 2, 3, 8, and 9) had detectable disease on CT imaging. All had been treated with total thyroidectomy, plus at least 150 mCi 131-iodine. All had biochemical evidence of persistent/recurrent disease with Tg > 2.0 ng/mL.
| Patient | Age (y) | Age at Dx (y) | Gender | Pathology | Metastatic sites | Persistence by CT imaging | Tg pre-Rx (ng/mL) | Tg post-Rx (ng/mL) | TSH pre-Rx (µU/mL) | TSH post-Rx (µU/mL) | Metformin (mg/day) |
|---------|---------|---------------|--------|-----------|------------------|---------------------------|-------------------|-------------------|-------------------|-------------------|--------------------|
| 1       | 56      | 34            | M      | PTC       | Neck lymph nodes; lung | Lung nodule: 3.2 cm, 0.8 cm; cervical mass: 2.3 cm; lung lymph nodes: 1.2 cm, 0.7 cm | 43.6 (S)          | 39.4 (S)          | 0.04              | 0.01              | 2000               |
| 2       | 79      | 65            | F      | FTC       | Lung              | Lung nodules: 0.7 cm, 0.5 cm | 9.5 (B)           | 7.4 (B)           | 0.03              | 0.03              | 1000               |
| 3       | 73      | 52            | M      | PTC       | Neck lymph nodes; lung | Lung nodules: 1.9 cm, 1.6 cm, 1.6 cm, 1.9 cm, 1.6 cm | 769 (B)           | 647 (B)           | 0.01              | 0.04              | 2000               |
| 4       | 70      | 64            | F      | PTC, TCvar | Neck lymph nodes; lung | No measurable lesions | 3.3 (B)           | 2.7 (B)           | 0.03              | 0.04              | 2000               |
| 5       | 31      | 25            | M      | PTC       | Neck lymph nodes | No measurable lesions | 10.9 (B)          | 7.9 (B)           | 0.04              | 0.04              | 500                |
| 6       | 72      | 64            | M      | PTC       | Neck lymph nodes | No measurable lesions | 8.3 (B)           | 9.9 (B)           | 0.04              | 0.02              | None               |
| 7       | 53      | 46            | F      | PTC       | Neck lymph nodes | No measurable lesions | 2.9 (B)           | 3.7 (B)           | 0.02              | 0.02              | None               |
| 8       | 90      | 60            | F      | FTC       | Neck lymph nodes; lung | Supraclavicular lymph node: 3.2 cm | 93 (B)            | 122 (B)           | 0.23              | 0.31              | None               |
| 9       | 86      | 75            | F      | HCTC      | Neck lymph nodes; lung | Lung nodules: 1.9 cm, 1.5 cm, 0.9 cm; neck: 6.2 cm, 2.6 cm | 5101 (B)          | 5510 (B)          | 0.02              | 0.02              | None               |
| 10      | 61      | 59            | F      | PTC       | Neck lymph nodes | No measurable lesions | 11.3 (B)          | 11.4 (B)          | 0.03              | 0.04              | None               |

Baseline characteristics of the control and metformin-treated patients. Measurements of persistent lesions are reported in the longest dimension.

Abbreviations: (B) indicates that Tg was measured by the Beckman chemiluminescent method; (S) indicates the Tg was measured by the Siemens chemiluminescent method; FTC, follicular thyroid cancer; HCTC, Hurthle cell thyroid carcinoma; PTC, papillary thyroid cancer; TCvar, tall cell variant of PTC; Tg pre-Rx, baseline serum thyroglobulin concentration prior to starting metformin.
The effect of metformin on Tg is shown for each of the metformin-treated patients and control patients in Fig. 1A, and summarized for each group in Fig. 1B. Following the initiation of metformin, Tg fell by 21.7 ± 8.4% (mean ± SD) over a period of 2 to 5 months. In contrast, the Tg rose by 17.4 ± 14.9% in all 5 of the control patients. The change in Tg of the metformin-treated patients was significantly different than that of the control patients (P < .01; Mann–Whitney test).

TSH, a known NMTC growth factor, did not change significantly with metformin therapy. In the 5 patients taking metformin, the serum TSH concentration was 0.030 ± 0.012 mIU/L prior to therapy and 0.027 ± 0.015 mIU/L while on metformin (P = NS). Similarly, TSH for the control group did not change significantly during the study period (0.048 ± 0.047 mIU/L vs 0.064 ± 0.093 mIU/L; P = NS). The mean decrease in weight during metformin therapy was 2.5 ± 1.7 kg (P = .1).

One patient (Patient 1) agreed to repeated Tg analysis. Figure 2 demonstrates the patient’s Tg over 35 months. Since metformin was withheld for about 6 days before and 2 days after CT imaging with contrast to avoid renal damage, we had the opportunity to observe the effect of repeated metformin withdrawals and challenges on Tg. There was a small but reproducible increase in Tg on all 5 metformin withdrawals and decrease in Tg with all 6 metformin challenges, as expected for a drug effect. The change in Tg occurred in approximately 6 days. TSH was <0.05 mIU/L throughout this entire period and did not change significantly with metformin withdrawal and challenge. In this single patient, the Tg doubling time (Siemens assay) was 2.5 years prior to the institution of metformin, and the projected Tg doubling time (Beckman Coulter assay) was 3 years during metformin therapy.

Two of the metformin-treated patients (Patients 1 and 3) with CT detectable disease elected to continue the metformin therapy, and CT imaging was analyzed according to RECIST 1.1 criteria. There was no evidence of tumor regression. Patients 1 and 3 demonstrated a progression-free survival of 10 months and 6 months, respectively. A third metformin-treated patient (Patient 2) had <1-cm lung nodules that were not large enough to be evaluated by RECIST 1.1 criteria, but these nodules remained stable for 38 months. None of our control patients were evaluable by RECIST 1.1 criteria, since they did not have frequent imaging. However, similar historical controls have progression-free survival of 3.6 to 5.8 months [13, 14].

**Discussion**

In this retrospective interventional study, we tested the hypothesis that metformin administration decreases Tg, a marker for tumor burden, in persistent/recurrent NMTC patients who had exhausted conventional therapies, including total thyroidectomy and 131-iodine. In patients with persistent/recurrent NMTC who are not undergoing any current therapy, the expectation is that Tg will gradually increase, as was seen in each of the control patients. In contrast to this expectation and to the control group, Tg decreased in all 5 patients treated with metformin. Within the limitations of the assay, the TSH did not change following the administration of metformin. Metformin has been reported to reduce TSH in hypothyroid subjects with pretreatment TSH concentrations higher than our patients, and this effect may occur over a longer time.
period \cite{15, 16}. It seems unlikely that the Tg decrease was due to a decrease in TSH, a known NMTCT growth factor. Further evidence of a metformin effect on Tg comes from the repeated metformin withdrawal and challenge design in Patient 1. Within 6 days of metformin withdrawal Tg increased, and within 6 days of the metformin challenge Tg decreased. In summary, metformin causes a TSH-independent decrease in Tg. In the 2 metformin-treated patients evaluable by RECIST 1.1 criteria, there was no evidence of tumor regression. Progression-free survival times were 6 and 10 months, which may be longer than the reported range of progression-free survival in similar historical controls of 3.6 to 5.8 months \cite{13, 14}. It is possible that our data underestimate the time to progression, since CT scans of the historical controls were performed in 2-month intervals \cite{13, 14}, while our 2 patients had CT scans performed approximately every 6 months. The Tg doubling time is a surrogate marker for tumor progression \cite{17, 18}. In the 1 patient with sufficient data to compare Tg doubling time with and without metformin, the Tg doubling time with metformin is about twice as long as prior to metformin initiation. Unfortunately, the Tg assays were different, and this was a single patient, so that caution should be exercised in interpreting this finding. Although our small sample size is insufficient for statistical comparison of disease-free progression and Tg doubling times, it is consistent with the hypothesis that metformin slows NMTCT progression and provides preliminary results that may be useful in designing larger prospective trials to determine whether metformin has a beneficial effect in persistent/recurrent NMTCT.

Metformin is a frequently used medication to treat type 2 diabetes, a disorder with high prevalence. Regardless of its effect on tumor burden and progression, the observation that metformin decreases Tg is important clinical information for physicians caring for type 2 diabetic patients with NMTCT.

Two observations strongly suggest a cause and effect relationship using a small number of patients. First, the study design is interventional. Other studies in humans are based on retrospective associations \cite{8, 9} that cannot establish cause and effect. Second, in the single patient with repeated Tg measurements following thyroglobulin withdrawal and challenge, the effect of metformin on Tg was observed repeatedly. Therefore, we were able to conclude that metformin likely decreases Tg.

The study design has a number of weaknesses that might be expected to result in a Type 2 error. The choice of the metformin dose varied from 500 to 2000 mg/day. The timing of endpoint measurements was variable both before and following metformin therapy. These variations are a function of a study in which each clinician negotiated with the patient and with the patient’s insurance carrier about when the different studies would be performed and how much metformin would be administered. All patients were restricted by a variety of personal, social, and financial issues that influenced the timing of repeat serum measurements and imaging. Therefore, we were unable to compare time to progression and Tg doubling time in the control and treatment groups. Furthermore, the small number of eligible patients limited the power of the study. The study patients included 3 distinct pathologic subtypes of NMTCT that might have responded differently. Despite the potential for a Type 2 error, a statistically significant difference in the primary endpoint was observed. Therefore, it seems likely that the decrease in Tg effected by metformin will be a reproducible finding in future studies.

Although this study establishes the key observation that metformin decreases Tg in NMTCT, the small sample size does not establish the frequency with which similar patients will respond. All 5 treated patients responded to metformin with a decrease in Tg, so the greatest likelihood is that most patients with persistent/recurrent NMTCT will also respond. However, the exact percentages and the degree of response will be determined in larger studies.

The mechanism(s) by which metformin reduces Tg is not known. There could be an increased clearance of thyroglobulin from the serum or decreased production of thyroglobulin by the NMTCT. Metformin is not known to affect the clearance of any proteins, so there is no obvious reason to believe that it increases thyroglobulin clearance. Metformin may decrease thyroglobulin production by either indirect and/or direct mechanisms. Metformin may have an indirect effect on NMTCT and thyroglobulin by decreasing glucose production and subsequent insulin secretion. These are well-known effects of metformin \cite{12}; in our metformin-treated patients, there was slight weight loss that would be expected to reduce insulin resistance and insulin secretion. As with many malignancies, obesity, insulin resistance, and hyperinsulinism may contribute to the pathogenesis of NMTCT \cite{19}. Alternatively, metformin may have a direct effect on NMTCT. Metformin decreases glucose production by inhibiting glycerol-3-phosphate dehydrogenase 2, which shuttles NADH into the mitochondria, subsequently lowering the intramitochondrial NAD/NADH ratio \cite{20, 21}. The CGAP public database indicates that glycerol-3-phosphate dehydrogenase 2 is expressed in normal thyroid and NMTCT at a higher level than in the liver, the classic metformin target. Therefore, metformin may lower the intramitochondrial NAD/NADH ratio in NMTCT. Lowering this ratio inhibits the metastatic spread of epithelial cell tumors in a mouse ectopic breast cancer model and a mouse ectopic thyroid cancer model \cite{11, 22}. Furthermore, metformin has been shown to increase the AMP-activated protein kinase, subsequently inhibiting mammalian target of rapamycin kinase, an essential component of the PI3K/AKT signaling complex, that is overexpressed in thyroid carcinomas \cite{12, 23, 24}. Everolimus, another mammalian target of rapamycin inhibitor, may have efficacy in NMTCT \cite{25}. In summary, there are plausible indirect and direct mechanisms by which metformin may affect NMTCT and Tg.

**Conclusion**

Metformin caused a TSH-independent reduction of Tg in patients with persistent/recurrent NMTCT. Larger prospective trials to evaluate metformin’s clinical benefit should be considered.

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**Author Contributions**

Each author contributed significantly to the study design and interpretation of the results. C.C. is the primary author of the
manuscript, and contributed to data analysis, theorizing of the metformin mechanism of action, and writing of the manuscript. P.T.P. and C.S. contributed to radiographic interpretation of progression-free survival. B.T. contributed patients to this study. D.M.M. is responsible for researching and explaining the potential mechanisms of metformin action. C.D.M. oversaw the study and contributed equally to each stage of the project.

Disclosures
The authors have nothing to disclose.

Data Availability
Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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