

FOUNDED 1923

Editor-in Chief

Jerome M. Hershman, MD VA Greater Los Angeles Healthcare System and UCLA School of Medicine Endocrinology 111D 11301 Wilshire Blvd Los Angeles, CA 90073 Telephone: 310-268-3852 Fax: 310-268-4879 Email: clinicalthyroidology@thyroid.org

Associate Editors:

Albert G. Burger, MD Professor, University of Geneva Geneva, Switzerland Email: clinicalthyroidology@thyroid.org

Stephanie L. Lee, MD, PhD

Director of the Thyroid Health Center Boston University Medical Center Boston, MA Telephone: 617-638-8530 Fax: 617-638-7221 Email: clinicalthyroidology@thyroid.org

Jorge H. Mestman, MD

Professor of Clinical Medicine and OB/GYN University of Southern California Keck School of Medicine Los Angeles, CA Telephone: 323-442-6179 Email: clinicalthyroidology@thyroid.org

Stephen W. Spaulding, MD

Department of Medicine, University of Buffalo Buffalo NY Telephone: 716-862-6530 Fax: 716-862-6526 Email: clinicalthyroidology@thyroid.org

President

Gregory A. Brent, MD Secretary/Chief Operating Officer Richard T. Kloos, MD

Treasurer David H. Sarne, MD

President-Elect James A. Fagin, MD

Secretary-Elect John C. Morris, MD

Past-President Terry F. Davies, MD

Executive Director

Barbara R. Smith, CAE American Thyroid Association 6066 Leesburg Pike, Suite 550 Falls Church, VA 22041 Telephone: 703-998-8890 Fax: 703-998-8893 Email: thyroid@thyroid.org

Designed By

Karen Durland (kdurland@gmail.com) Clinical Thyroidology Copyright © 2011 American Thyroid Association, Inc.

American Thyroid Association, Inc. Printed in the USA.All rights reserved.

Clinical THYROIDOLOGY

VOLUME 23 • ISSUE 6

JUNE 2011

METFORMIN SHRINKS THYROID NODULES IN PATIENTS WITH INSULIN RESISTANCE

Rezzonico J, Rezzonico M, Pusiol E, Pistoia F, Niepomniszcze H. **Metformin treatment for small benign thyroid nodules in patients with insulin resistance.** Metab Syndr Relate Disord 2011;9:69-75. Epub December 3, 2010.

BACKGROUND

In a prior study, these authors found that individuals with hyperinsulinemia had an increased thyroid volume as well as an increased number of thyroid nodules.

METHODS

Eighty women who were thyroid peroxidase antibody-negative and living in an iodine-sufficient area and who had insulin resistance (IR) and solid, benign, hyperplastic thyroid nodules were prospectively evaluated for nodule shrinkage using metformin, levothyroxine, or a combination of the two. Fourteen women did not complete follow-up, leaving 66 women with 75 thyroid nodules. IR was evaluated by homeostasis model assessment (HOMA; fasting serum insulin in microunits per milliliter multiplied by plasma glucose in millimoles per liter divided by 22.5); a HOMA index of >2.5 indicated IR. Nodule volume determined using ultrasound was calculated with the elliptical shape volume formula. Women who qualified were randomly assigned to four treatment groups and followed for 6 months: group 1 (n = 14; 19 nodules) was treated with metformin alone; group 2 (n = 18; 21 nodules) was treated with metformin and levothyroxine; group 3 (n = 19; 20 nodules) was treated with levothyroxine alone; and group 4 (n = 15; 15 nodules) were controls. The metformin dose was 1000 mg twice daily; the dose of levothyroxine was adjusted to keep the serum thyrotropin (TSH) level at 0.11 to 0.99 mU/L. Patients were treated for 6 months and then reevaluated using ultrasound.

RESULTS

The characteristics of the patients in the groups were similar at baseline (mean age, 43; mean weight, 80 kg; mean body-mass index [the weight in kilograms divided by the square of the height in meters], 31; mean HOMA score, 3.3; mean TSH, 2.55; median nodule volume, 298 mm³). Patients treated with levothyroxine had a significant decrease in TSH (mean, 0.59 mU/L). Patients taking metformin had a significant decrease in their HOMA scores into the normal range. All patients on active treatment (groups 1 to 3) had

continued on next page

METFORMIN SHRINKS THYROID NODULES IN PATIENTS WITH INSULIN RESISTANCE

a significant reduction in thyroid volume, with no significant difference in the posttreatment thyroid volume between these three groups. Nodule size was markedly and significantly reduced in both groups treated with metformin (from 364 to 75 mm³ in group 1 and from 336 to 126 mm³ in group 2; 74% of nodules were reduced with metformin alone, 95% were reduced with metformin plus levothyroxine treatment), whereas nodule size was unchanged in the other treatment groups. Patients treated with metformin alone had a significantly greater reduction in nodule size than those treated with levothyroxine

alone or those with no treatment. Similar nodule shrinkage with metformin was seen with small (<1 cm) and larger lesions (1 to 2 cm).

CONCLUSIONS

In patients with small hyperplastic thyroid nodules, metformin produced a significant decrease in nodule size, and the combination of metformin plus levothyroxine showed the best reduction in nodule volume, whereas levothyroxine alone reduced nodule growth but not nodule volume.

This small, relatively brief study reveals a marked reduction in thyroid nodule volume in 74% of these insulin-resistant subjects who were being treated with metformin. The overall reduction in thyroid volume was less impressive, perhaps because only small lesions were included in this study, hence making up a relatively small percentage of total thyroid volume. Combination therapy with metformin plus levothyroxine was associated with a reduction in nodule size in 95% of lesions. In contrast, suppressive therapy with levothyroxine alone did not result in nodule shrinkage, perhaps because the TSH suppression was briefer and TSH was not suppressed to grossly hyperthyroid levels as has been done in prior successful trials (1,2). Past studies evaluating shrinkage of thyroid nodules with levothyroxine suppression have had mixed results, and the

References

1. Wémeau J, Caron P, Schvartz C, et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular no palpable changes: a randomized, doubleblind, placebo-controlled trial by the French Thyroid Research Group. J Clin Endocrinol Metab 2002;87:4928-34. 2009 American Thyroid Association management guidelines for thyroid nodules do not recommend levothyroxine suppressive therapy for patients with benign nodules who live in iodine-sufficient areas (3). In this study, metformin treatment appears to offer a tantalizing reduction in thyroid nodule volume, with efficacy seen in a striking percentage of treated patients. As insulin-resistant patients often have multiple associated risk factors for surgery, this would be an important group for further study of non-operative therapies, especially for larger nodules in which cosmesis may be an issue. As the authors point out, we need more studies done with metformin to reproduce these results.

— Jane Weinreb, MD

Division of Endocrinology, Diabetes and Metabolism VA Greater Los Angeles Healthcare System Los Angeles, CA 90073

- 2. Papini E, Petrucci L, Guglielmi R, et al. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. J Clin Endocrinol Metab 1998;83:780-3.
- 3. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.