Idiopathic inflammatory myopathies and hypertension: Possible involvement of hormonal factors

Decio Armanini MD, PhD\(^1\) | Chiara Sabbadin MD, PhD\(^1\) | Luciana Bordin PhD\(^2\)

\(^1\)University of Padua, Department of Medicine, Padua, Italy
\(^2\)University of Padua, Department of Molecular Medicine-Biological Chemistry, Padua, Italy

Correspondence: Decio Armanini, Department of Medicine - Endocrinology, University of Padua, Via Ospedale 105, 35100 Padua, Italy.
Email: decio.armanini@unipd.it

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Qin et al\(^1\) developed a predictive model for the assessment of hypertension associated with idiopathic inflammatory myopathies (IIMs). Fifty-four patients with IIMs with a diagnosis of new-onset hypertension and 308 normotensive controls with the same diseases were studied. The authors found age, diabetes, and triglycerides as predictors of hypertension and concluded that this assessment could be used in the clinic to predict and treat patients likely to experience hypertension associated with IIMs and to prevent future cardiovascular risk. In addition to the possibility of using the nomogram to predict the onset of hypertension, the study is also interesting in trying to explain why patients with myositis have a higher risk of becoming hypertensive than the general population, as also reported by the study of Limaye.\(^2\) The finding that hypertensive patients are older than normotensive controls with IIMs confirms the need to consider the nomogram proposed by the authors to treat patients who may develop hypertension. However, some of the parameters reported in the study need careful evaluation when interpreting the results. The study did not measure potassium, calcium, renin, aldosterone cortisol, and especially serum creatine phosphokinase, which is usually an important index in inflammatory myopathies and muscle suffering. The study also excluded patients with previous history of primary hyperaldosteronism and Cushing's syndrome, two diseases that are often associated with myopathies, sometimes autoimmune. Recent studies, however, have shown that it is not the aldosterone value but the aldosterone-renin ratio that is the most important index of increased aldosterone action. It has been observed that in some cases of inflammatory diseases, as for example polycystic ovary syndrome, the aldosterone-renin ratio is higher than in controls, although remaining in the normality range.\(^3\)

1 | INFLUENCE OF TREATMENT OF THE CLINICAL AND BIOCHEMICAL EVALUATION

The values of some parameters considered in the nomogram could also be influenced by current therapies. The average blood pressure values in the hypertensive group seem, in some cases, within the normal range (mean ± SD: 134 ± 16 and 85 ± 13), assuming that some patients with new-onset hypertension were treated at the time of evaluation and perhaps also triglyceride values could be influenced by glucocorticoid therapy or by the association with obesity or metabolic syndrome that is frequently associated with hypertension and cardiovascular disease.

2 | EFFECT OF GLUCOCORTICOID TREATMENT AT THE LEVEL OF MINERALOCORTICOID AND GLUCOCORTICOID RECEPTORS

A possible hypothesis is therefore that therapy of IIMs is somehow involved in the genesis of hypertension in some patients predisposed to hypertension. This hypothesis is supported by the high percentage of patients treated with glucocorticoids. The authors found that the percentage treated with glucocorticoids was similar and concluded that therapy does not influence the interpretation of results and the nomogram derived. An alternative hypothesis is that the therapy of IIMs is involved in the genesis of hypertension in patients perhaps already predisposed. Treatment with glucocorticoids has both a suppressive action on adrenocorticotropic hormone

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secretion and a direct action at the level of glucocorticoid receptors. Many glucocorticoids are also a substrate of 11β-hydroxysteroid dehydrogenase 2 (11HSD2) in the kidney and classic tissue targets of aldosterone. Some glucocorticoids also have an affinity for the mineralocorticoid receptor, and the type of glucocorticoid used is not described in the reported study. It is known that the affinity of cortisol for aldosterone receptors is like that of aldosterone and that aldosterone binds to its receptor in cells of classical target tissues only due to 11HSD2-mediated intracellular inactivation of cortisol to cortisone. In stressful situations, it has been shown that the cellular inflammatory state may accentuate a possible mineralocorticoid action of cortisol or of other glucocorticoids. In immunocompetent cells, it is important to consider the relationship between glucocorticoid receptors and mineralocorticoid receptors and the presence of the type 1 11HSD. This enzyme activates cortisone to cortisol, allowing its prevalent binding to the glucocorticoid receptor, which is present in 40-fold greater amounts than mineralocorticoid receptors in immunocompetent cells. In situations of inflammation, a role of mineralocorticoid receptors could be hypothesized also in these non-classical target tissues of aldosterone. However, most administered glucocorticoids act only on the glucocorticoid receptor, improving the anti-inflammatory response and reducing the inflammatory reaction due to the binding of endogenous cortisol to mineralocorticoid receptors. An excess of glucocorticoids also reduces the autoimmune response. Adrenocorticotrophic hormone blockade thus plays an important role in autoimmune and inflammatory diseases, but it could reduce the immune response to viral pathology. Glucocorticoid therapy may also make the interpretation of antinuclear antibodies and triglyceride assessment difficult.

3 | AUTOIMMUNITY, ANGIOTENSIN 2 TYPE 1 RECEPTORS, AND ALDOSTERONE

Both previous and current studies have hypothesized the involvement of a possible autoimmune mechanism in the genesis of hypertension in patients with IIMs, such as the presence of antibodies to alpha1 adrenergic receptors and angiotensin II type-1 receptor. These mechanisms could be related to an inflammatory reaction dependent on the autoantigens of autoimmune myositis. Recent studies have shown an important role of autoimmunity in primary hyperaldosteronism, preeclampsia, and other autoimmune diseases. The association between autoimmunity and hypertension has been considered in previous works especially considering that aldosterone is the main pro-inflammatory and autoimmune-inducing hormone. Recently, it has been shown that in inflammatory diseases, the aldosterone-renin ratio is often higher than in healthy controls, as for example in polycystic ovary syndrome. A previous study observed that aldosterone accentuates the progression of experimental autoimmune encephalomyelitis that is induced by T helper 17 lymphocyte activation and this effect is attenuated by administration of mineralocorticoid receptor blockers. Aldosterone directs the differentiation of naive lymphocytes into T helper 17 lymphocytes that are involved in autoimmunity and in subsequent inflammatory damage, hypertension, and related pathologies. In a previous study, we showed that lymphocytes possess aldosterone receptors and that incubating lymphocytes with aldosterone induces the protein synthesis of PAI 1 and p22phox, two markers of inflammatory status, and that this effect is blocked by coincubation with canrenone, the principal metabolite of spironolactone.

An indirect demonstration of the inflammatory effect of aldosterone has been shown since the discovery of aldosterone when it was hypothesized that the steroid has an action opposite to that of cortisol and this hypothesis was supported by the improvement of inflammatory manifestations of rheumatoid arthritis by administering spironolactone. This drug has a potent anti-inflammatory action even in patients without hyperaldosteronism, as shown by Pitt’s studies. It has been shown that spironolactone and eplerenone are useful drugs to prevent cardiovascular risk both in hypertensive patients and in patients who have had a cardiovascular or cerebrovascular accident. The use of spironolactone should have more support in therapy given the involvement of aldosterone in hypertension and autoimmunity.

4 | CONCLUSIONS

The current study is important because it encouraged continued research on the relationship between autoimmunity hypertension cardiovascular complications and possible therapies to prevent these consequences of these pathologies. It would be interesting to evaluate whether autoimmune pathology and hypertension have a common origin that could be an inflammatory state that predisposes to the activation of hormones stimulating autoimmunity. The study is preliminary and needs evaluation of many more cases, assessment of muscle and hormonal parameters related to myositis. In addition, it would be necessary to evaluate the impact of each drug used alone or in combination on the immune, metabolic, cardiovascular, and renal aspects and whether the therapy can in some way, if started at a young age, reduce the risk of hypertension and its complications, or whether it can worsen some risk parameters in these patients, even if it cures myositis.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

DA, CS, and LB contributed to the conception of the work and interpretation of published data, drafted the manuscript, revised it critically, and gave the final approval of the version to be published.

ORCID

Decio Armanini https://orcid.org/0000-0002-6433-5155
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