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Coexistence of hypertension and antinuclear antibodies: High blood pressure as a potential risk factor for autoimmunity

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MAIN POINTS

- HT may contribute to vascular stress and low-grade inflammation, which could potentially facilitate the development of autoantibodies.
- Approximately 50% of hypertensive patients were found significantly positive for ANAs (anti-dsDNA, anti-ENA, and anti-Hep-2 nucleus).
- This finding confirms previous reports of an association between HT and autoantibodies, and further suggests that hypertensive patients should be monitored for potential autoimmune conditions.

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ABSTRACT

Aim: Hypertension (HT) is characterized by endothelial damage, vascular wall stress, and inflammation, potentially fostering autoantibody production. The prevalence of antinuclear antibodies (ANAs), common autoantibodies associated with systemic autoimmune diseases, remains unclear in non-autoimmune conditions like HT. This study aimed to investigate the presence of ANAs (anti-dsDNA, anti-ENA, anti-Hep-2 nucleus) in HT patients and compare these findings with healthy individuals.

Materials and Methods: This experimental case-control study included 32 hypertensive patients (7 men, 25 women; age 48.9 ± 6.6) and 32 age- and gender-matched healthy controls (7 men, 25 women; age 48.0 ± 5.2). HT status was self-reported based on prior diagnoses. ANAs, including anti-dsDNA, anti-ENA, and anti-Hep-2 nucleus antibodies, were measured using validated ELISA kits.

Results: Body mass index (BMI) and ages were comparable between groups (p>.05). Median ANA index values and positivity rates (%) for hypertensive and healthy groups were: anti-dsDNA [1.25 (59.4%) vs. 0.8 (28.1%)], anti-ENA [0.92 (46.9%) vs. 0.64 (21.9%)], and anti-Hep-2 nucleus [0.93 (43.8%) vs. 0.84 (18.8%)]. All three ANA tests showed significantly higher ANA levels and positivity rates in the hypertensive group compared to controls (p<0.05).

Conclusion: Our findings indicate higher ANA levels and positivity rates in individuals with HT compared to healthy controls, suggesting a potential link between HT and autoantibody production. Further long-term prospective studies are needed to determine the clinical significance of this elevated ANA frequency and the potential role of these antibodies in the development of autoimmune diseases.

Keywords: Hypertension, Antinuclear antibody, dsDNA, ENA

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INTRODUCTION

Hypertension (HT), characterized by persistently high blood pressure, is a major global health issue significantly contributing to the burden of cardiovascular diseases, stroke, and kidney failure. Approximately 3.5 billion adults worldwide are at risk of HT, making it a leading risk factor for global disease burden and mortality [1]. This condition accounts for 9.4 million deaths and 212 million disability-adjusted life years (DALYs) lost annually, representing 8.5% of the global disease burden [2]. The pathogenesis of HT is complex and multifactorial, involving genetic predisposition, age, obesity, sedentary lifestyle, and high-sodium diets [3-5].

Autoantibodies, produced by the immune system to target the body's own tissues, play a key role in autoimmune disorders. Around 5-7% of the global population is affected by autoimmune diseases linked to these autoantibodies, accounting for 0.5-2% of all deaths [6]. Among them, antinuclear antibodies (ANAs) bind to intracellular components such as the nucleus, DNA, RNA, and centromeres, contributing to cellular dysfunction, inflammation, and tissue damage [7,8]. ANAs are broadly classified into two main subgroups: anti-dsDNA, which targets genetic material, and anti-ENA (extractable nuclear antigens), which targets various intracellular components.

While commonly associated with autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome,

and rheumatoid arthritis, ANAs have also been detected in individuals without a diagnosed autoimmune condition [9]. Notably, ANA positivity has been reported in various chronic disorders, including type 2 diabetes, chronic kidney disease, and cardiovascular diseases [10-12]. These conditions often share common features such as persistent low-grade inflammation and tissue injury, which may trigger non-specific immune activation and lead to the production of autoantibodies [13].

Similarly, HT is characterized by chronic vascular wall stress, endothelial damage, and sterile inflammation—conditions that may create a microenvironment conducive to immune activation [14,15]. These processes could expose normally sequestered nuclear antigens to the immune system, potentially triggering ANA production in susceptible individuals. In this context, we hypothesized that ANA levels might be elevated in individuals with HT compared to normotensive individuals. The aim of our study was to determine the prevalence of ANA positivity in patients with HT and to compare it with healthy controls, in order to explore potential immunological features associated with HT.

MATERIALS AND METHODS

This study for ethical approval was obtained from the Bingöl University Health Sciences Scientific Research and Publication Ethics Committee (2025-25/1).

Sample size determination

The sample size was determined using the G*Power software program [16]. A power analysis for two independent groups (independent t-test) indicated that with a Type I error (α) of 0.05, a Type II error (β) of 0.20 (Power = 0.80), a large effect size (f = 0.75), and equal group sizes, a minimum of 29 participants per group would be required [17,18].

Study design and participants

This study was designed as a case-control study, involving 32 hypertensive individuals (7 men, 25 women; mean age 48.9 ± 6.6 years) and 32 age- and gender-matched healthy controls (7 men, 25 women; mean age 48.0 ± 5.2 years). The presence of HT in patients was determined based on previous diagnoses and self-reports. Control group participants were selected based on self-reported healthy status, including individuals who stated no known chronic diseases or previous medical diagnoses.

Among the 32 individuals in the HT group, 16 had additional chronic conditions such as DM, cardiovascular diseases (e.g., venous insufficiency, arrhythmia), asthma, thyroid disorders, chronic lung disease, hepatitis B, endometrial cancer, or polycystic ovary syndrome (PCOS). To allow for clearer interpretation of the autoantibody results, individuals with HT but without any additional chronic diseases were also evaluated separately.

Determination of ANA positivity

ANA levels were measured using three different validated ELISA test kits: anti-dsDNA, anti-ENA, and anti-Hep-2 nucleus [19,20].

- The anti-dsDNA assay utilized purified double-stranded calf thymus DNA as the antigen.
- The anti-ENA kit included multiple specific antigens (Sm, nRNP, La/SS-B, and Jo-1).
- The anti-Hep-2 nucleus kit was based on whole-cell nuclear extracts derived from the HEp-2 cell line (ATCC, CCL-23).

The sensitivities for the anti-dsDNA, anti-ENA, and anti-Hep-2 nucleus tests were 93.8%, 83.3%, and 90%, respectively, while their specificities were 91.7%, 83.3%, and 87.5%, respectively [19]. The intra- and inter-assay coefficients of variation for these tests were 7.8%, 7.5%, and 9.9%, respectively [19].

All procedures followed the kit protocols. Serum samples were diluted 1/100 and added to the wells alongside negative and positive control samples. Subsequently, anti-human IgG conjugated with biotin and streptavidin peroxidase was added. Plates were washed three times with 0.05% Tween-20 before each solution addition. Finally, a chromogenic substrate (tetramethylbenzidine, TMB) was added, and the reaction was halted with 11% H_2SO_4. Plates were read using a spectrophotometer at 450 nm.

Calculation of ANA results

The cut-off value for positivity was determined using the cut-off control, as described in the kit protocol. It was calculated using the formula: average OD of negative controls + 3 standard deviations (SD). Sample OD values were converted to an antibody index (Ab index) using the formula: Ab index = Sample OD / Cut-off OD. Values <1.0 were classified as ANA IgG negative, while values $\geq$1.0 were classified as ANA IgG positive. The test was deemed valid if the Ab index of the positive control was >1.1 and the negative control was <0.9.

Statistical analysis

The normality of the data was assessed using the Shapiro–Wilk test. Age and BMI, which were normally distributed, were compared between groups using the independent samples t-test. ANA levels did not follow a normal distribution; thus, they were compared between the hypertensive and control groups using the Mann-Whitney U test. The Mann-Whitney U test was also employed for the comparison of ANA positivity in hypertensive patients without comorbid chronic diseases. For categorical variables, comparisons were made using the chi-square (χ^2) test. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

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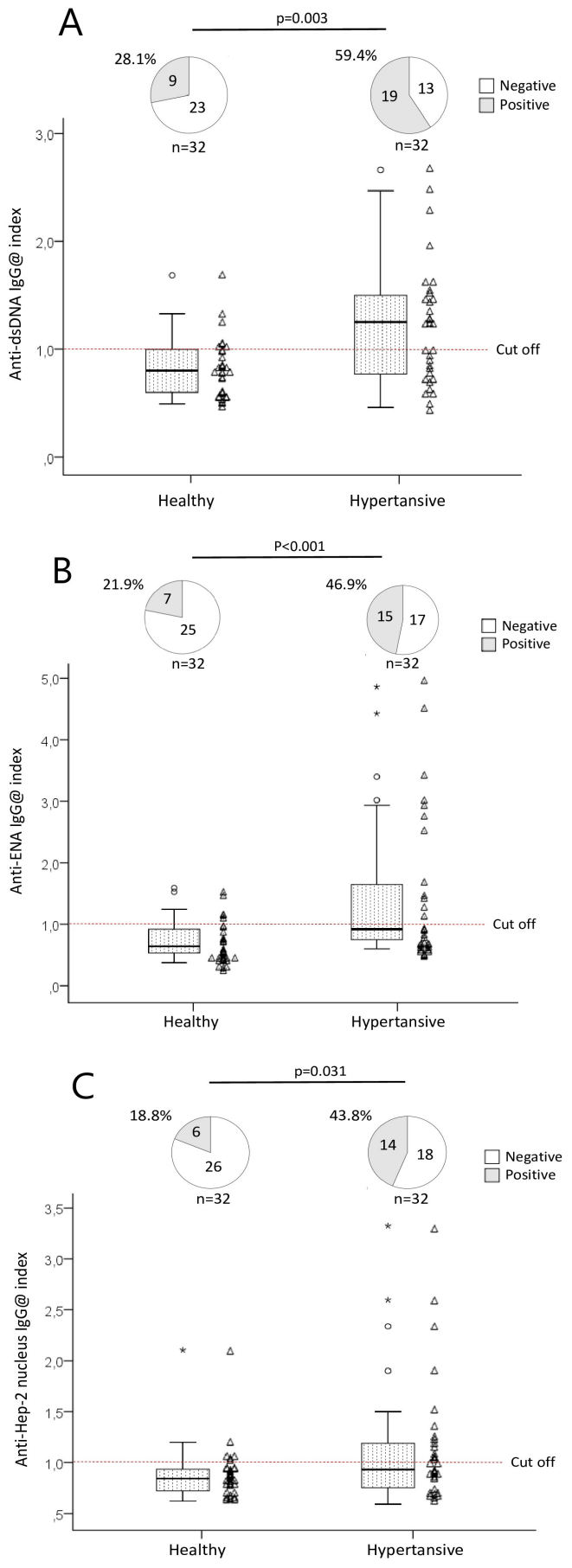

Figure 1. The anti-dsDNA (A), anti-ENA (B), and anti-Hep-2 nucleus (C) antibody levels and positivity percentages in hypertensive and healthy individuals. In all three assays, ANA levels in hypertansive individuals were found to be significantly higher compared to healthy individuals.

Table 1. Age of the BMI of the participants.

	HT (n=32)	Healthy (n=32)	p value
Age	48.0 ± 5.2	48.9 ± 6.6	0.419
BMI	29.1 ± 4.2	27.5 ± 4.2	0.206

RESULTS

The age and body mass index (BMI) distributions were comparable between the healthy and hypertensive groups (p>0.05) (Table 1). Among the 32 individuals with HT, 16 had isolated HT, while the remaining 16 had additional chronic conditions. These included 8 with DM, 6 with cardiovascular problems (e.g., venous insufficiency, arrhythmia), 2 with asthma, 2 with hypothyroidism, 2 with hyperthyroidism, 1 with hepatitis B, 1 with chronic lung disease, 1 with endometrial cancer, and 1 with PCOS.

Comparison of ANA levels between hypertensive and healthy individuals

In the anti-dsDNA test, 19 samples (59.4%) from the hypertensive group and 9 samples (28.1%) from the healthy group were positive (p = .003) (Figure 1A). For the anti-ENA test, 15 samples (46.9%) from the hypertensive group and 7 samples (21.9%) from the healthy group were positive (p<0.001) (Figure 1B). In the anti-Hep-2 nucleus test, 14 samples (43.8%) from the hypertensive group and 6 samples (18.8%) from the healthy group were positive (p = 0.031) (Figure 1C).

ANA positivity in hypertensive patients without comorbid chronic diseases

To mitigate potential confounding effects from other chronic diseases known to trigger ANA formation, we re-evaluated ANA positivity in the subset of 16 individuals with isolated HT. Among these patients, 10 (62.5%) tested positive for anti-dsDNA, 11 (68.8%) for anti-ENA, and 10 (62.5%) for anti-Hep-2 nuclear antibodies (Fig. 2). The frequency of these positive results was significantly higher compared to healthy individuals (p<0.05).

DISCUSSION

Our study, which investigated the relationship between HT and ANAs, revealed that nearly half of the hypertensive patients tested positive for ANAs. While ANAs are also found in healthy individuals [9], their elevated prevalence in our hypertensive cohort suggests a close relationship between HT and ANA positivity. This relationship is likely bidirectional, meaning HT could contribute to ANA development, and ANAs might potentially trigger HT [14, 21]. Although not yet fully understood, the possible link between HT and autoantibody production has been associated with mechanisms such as chronic inflammation, endothelial stress, oxidative injury, and genetic predisposition [22–25].

HT can lead to vascular wall damage and endothelial cell dysfunction, potentially initiating inflammatory responses and

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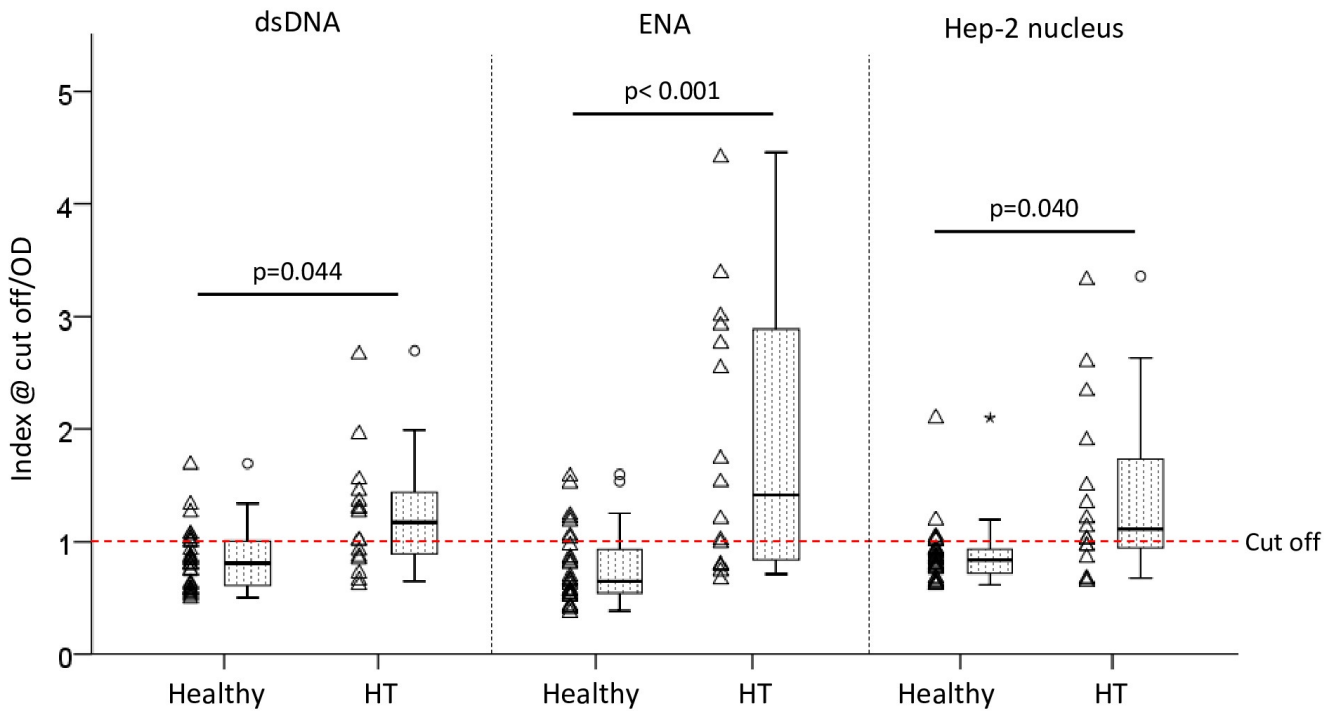

Figure 2. Comparison of ANA levels between hypertensive individuals without additional chronic conditions (n=16) and healthy controls (n=32). Among the hypertensive group, ANA positivity was observed in 62.5% for anti-dsDNA, 68.8% for anti-ENA, and 62.5% for Hep-2 nuclear antibodies. These rates were significantly higher compared to the healthy control group (p<0.05).

fostering chronic inflammation. Sung et al. observed elevated levels of C-reactive protein (CRP), a key inflammatory marker, in individuals with HT [23]. Similarly, Bautista et al. demonstrated that patients with higher levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were more likely to have HT [26]. During this inflammatory process, the immune system may begin to target the body's own structures as it continuously clears cellular debris from damaged cells and tissues, potentially leading to the production of autoantibodies like ANAs. Osmori et al. [27] suggested that chemically modified self-proteins, often found in inflamed tissues, are potential candidates for autoantibody production. Their study also noted that epitope spreading—the diversification of immune responses from the initial epitope to other epitopes on the same or different antigens—which can lead to autoantibody production, is frequently observed in the inflamed tissues of patients with rheumatoid arthritis [27]. This interplay between HT, inflammation, and autoantibodies may help explain the high ANA prevalence we observed in our hypertensive patients.

In our study, the high ANA production in hypertensive patients may also be linked to oxidative stress, a key mechanism in HT development [24]. Reactive oxygen species (ROS) are crucial for vascular wall homeostasis, but their increased production can contribute to HT pathophysiology [28-30]. This often coincides with reduced bioavailability of nitric oxide (NO) and antioxidants, a phenomenon observed in both experimental models and human HT. Free radicals can disrupt normal cellular functions, causing damage to DNA, proteins, and lipids. This oxidative damage and subsequent protein modifications may be linked to autoantibody pathogenesis. Kuruen et al. [31] demonstrated that oxidative modifications of proteins can trigger antibody production in various diseases, including SLE, alcoholic liver disease, DM, and rheumatoid arthritis (RA). Additionally, Ramani et al. [32] stated that immune responses against tissues and organs increase with oxidative stress, further exacerbating the pathobiology of autoimmune diseases. In this context, the interaction between oxidative stress, immune responses, and autoantibody production suggests that the high prevalence of ANAs in hypertensive patients could be related to oxidative stress.

Genetic factors have long been recognized as contributors to HT pathogenesis. Research indicates that several genes involved in vascular tone regulation, sodium balance, and the renin-angiotensin system are associated with an increased risk of HT development [33]. Furthermore, polymorphisms in genes encoding proteins involved in oxidative stress pathways, such as NADPH oxidase and superoxide dismutase, may predispose individuals to HT by exacerbating oxidative damage within the vasculature [34]. This heightened oxidative stress can lead to endothelial dysfunction, a hallmark of HT, which may in turn trigger inflammatory responses and autoantibody

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production.

Familial aggregation studies further support a shared genetic vulnerability, as HT and autoimmune diseases often co-occur in families [35]. This suggests common genetic factors might contribute to both conditions, either through a direct predisposition to immune dysregulation or via the inflammatory effects of HT on the immune system. Similarly, genetic susceptibility to autoimmune diseases, particularly through polymorphisms in immune-regulatory genes, has been linked to autoantibody production [36]. Emerging research highlights a genetic overlap between HT and autoimmune diseases, with certain genetic variants associated with both conditions [37]. This overlap may help explain the higher prevalence of autoantibodies, such as ANAs, observed in hypertensive patients.

Limitations

Our study has several limitations. Participants' HT status was based on self-reports of prior diagnoses rather than direct clinical measurements. While we specifically asked about medically diagnosed conditions to minimize recall bias, this method inherently carries some degree of subjectivity.

Furthermore, among the 32 individuals in the HT group, 16 had additional chronic conditions such as DM, cardiovascular diseases (e.g., venous insufficiency, arrhythmia), asthma, thyroid disorders, chronic lung disease, hepatitis B, endometrial cancer, or PCOS. These comorbidities could potentially influence immune-related parameters, including ANA levels, and were therefore considered a limitation. To mitigate this, subgroup analyses were performed, and ANA measurements were evaluated separately in hypertensive individuals with and without these additional chronic conditions.

Finally, due to limited information in patient files, our study could not include data on the duration of HT diagnosis, the healthcare provider responsible for the initial diagnosis, or whether the condition was being managed with medication.

CONCLUSION

The high prevalence of ANAs observed in hypertensive patients in our study may indicate an increased risk of autoimmunity. However, long-term prospective studies are essential to confirm this link and to determine the clinical significance of this finding. Chronic inflammation, oxidative stress, endothelial dysfunction, and genetic predisposition are among the potential mechanisms contributing to HT-associated ANA production. Further molecular and longitudinal studies are critically needed to clarify the underlying immunological pathways linking HT with autoantibody formation.

Ethics Committee Approval: Ethical approval was obtained from the Bingöl University Health Sciences Scientific Research and Publication Ethics Committee (2025-25/1).

Informed Consent: As this study was designed retrospectively, obtaining patient informed consent was not required.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that there are no conflicts of interest to disclose.

Author Contributions: FD: Conceptualization, Methodology, Validation, Formal analysis, Writing - Original Draft; SY: Formal analysis, Supervision, Project administration, Writing - Review & Editing

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