

Environmental and individual factors associated with protection and predisposition to autoimmune diseases

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ABSTRACT

Objective: This study aimed to correlate possible predisposing and protective factors involved with autoimmune diseases (ADs) in a Brazilian microregion.

Methods: This case-control study recorded 362 cases of ADs prevalent in the Águas Formosas microregion, state of Minas Gerais, Brazil, between January and December 2016, through the application of a questionnaire. Overall, 724 controls were randomly selected according to gender and age. Logistic regression was used to calculate the adjusted odds ratio (OR), confidence interval, and *P*-value to compare the strength of association between the variables of interest assessed.

Results: Individuals with Graves' disease (OR: 11.9977), followed by rheumatoid arthritis (RA), psoriasis, lupus, Hashimoto's thyroiditis (HT), and vitiligo, were strongly associated with the risk of developing the disease after the hepatitis B vaccine. Having consumed cow milk before 6 months of life was a factor associated only with psoriasis (OR: 0.3321) and RA (OR: 0.2880). Type 1 diabetes patients were associated only with surgical procedures (OR: 0.1160), just as physical and psychological traumas were associated only with vitiligo (OR: 5.9848). Contact with chemicals was more related to vitiligo (OR: 0.7142), RA, psoriasis, lupus, and thyroiditis. Physical exercise was the most significant protective factor for vitiligo (OR: 0.4904), followed by HT, RA, psoriasis, and lupus; and the consumption of filtered water with candles was a protective factor for vitiligo (OR: 0.3325).

Conclusion: The associations suggest that predisposing and protective factors for ADs play a pivotal role in their onset, enabling health management, control, and intervention of this population.

Keywords: Autoimmune diseases, behavioral factors, biological agents, chemical agents, dietary agents, environmental factors, molecular mimicry

Introduction

Autoimmune diseases (ADs) are characterized by loss of immunological tolerance to autoantigens, with several limiting conditions.^[1,2] Although the exact origin of this group of diseases is not known, there is evidence that its onset results from 30% genetic predisposition and the remaining 70% comes from extrinsic factors of which at least 50% of known autoimmune disorders are attributed to unknown triggering factors.^[3]

The occurrence and distribution of ADs are known to be affected by age, gender, ethnicity, geographical location, genetic background, and behavioral factors. However, the way how these factors directly influence the development of these diseases remains unknown.^[4,5] Hence, the importance of conducting studies on the association of systemic and organ-specific ADs with possible triggering factors through

human and animal models, to elucidate their causal link in several regions of the world that present different patterns of prevalence.^[6]

Epidemiological studies with high sensitivity and specificity were responsible for important findings such as the fact that iodine imbalance may accelerate the induction of Hashimoto's thyroiditis (HT),^[7] those that related ultraviolet radiation exposure,^[8] and procainamide use to systemic lupus erythematosus (SLE),^[9] which has associated the use of silicone prosthesis with polymyositis,^[10] in addition to associating the sting of hematophagous insects with endemic pemphigus foliaceus^[11] and, finally, the correlation of several factors such as pregnancy, puerperium, infection, general anesthesia, and use of other medications such as penicillamine, antimalarials, beta-blockers, verapamil, or aminoglycosides with myasthenia gravis.^[12]

Despite the increase in studies on predisposing factors for AD^[13-16] in more developed regions of the world, such as North America and Europe, in recent decades, on the other hand, these studies are scarce in different underdeveloped regions, such as Latin America and Africa. It is also noteworthy that among the etiological studies carried out to date, there are a greater number of those that address SLE, HT, and rheumatoid arthritis (RA),^[8,9,17] a reasonable number of studies addressing multiple sclerosis (MS) and systemic sclerosis (SSc);^[18,19] few studies on Sjögren's syndrome;^[20] and no study on immune thrombocytopenic purpura and antiphospholipid syndrome that do not even indicate their etiologies. Most case-control and cohort studies conducted to date come from study centers associated with universities, most of which address only one element of the causative factor of a pathological condition or a limited group of people with a restricted focus on one small collection.^[3]

National studies conducted in the country to date are scarce and outdated, and they have only addressed the relative prevalence of a limited number of ADs;^[21,22] however, there is no record in the literature of any association study conducted in the state of Minas Gerais or even in the country, which confirms the lack of data to compare the proportion of ADs in low-income areas such as the Mucuri Valley Mesoregion. In this context, the present study aims to correlate the findings with possible predisposing and protective factors involved in the etiopathogenesis of the most prevalent ADs to improve health management in this region and enable new perspectives on knowledge, control, and intervention.

Methods

This is epidemiological research with a quantitative approach followed by a retrospective case-control study.^[23] The research was carried out in the Águas Formosas Microregion, located in the northeast of Minas Gerais state. The microregion had an estimated total population of 60,413 inhabitants in 2016,^[24] with an approximate area of 4,150,700 km²,^[21] and is composed of eight municipalities: Águas Formosas, Bertópolis, Crisólita,

Fronteira dos Vales, Machacalis, Pavão, Santa Helena de Minas, and Umburatiba [Figure 1].

The study was conducted through active case search and review of medical records of all cases of patients with the confirmatory diagnosis of ADs of the 26 primary health care units of the Águas Formosas Microregion, from January to June 2016, carried out by professionals of the local medical archiving service previously trained to carry out the epidemiological survey. All patients who participated in the study were undergoing home or outpatient treatment, with no inpatients being included in the study.

As a data collection instrument, it was used the version of a script form prepared by the Ministry of Health^[25] used in health units to identify the physiological and pathological antecedents of patients and their families, being adapted to questions related to 20 variables associated with autoimmunity. The sociodemographic variables used were: (a) Gender, (b) age range, (c) education level, (d) marital status, (e) occupation, (f) area of origin, and (g) municipality of residence.

The questionnaire applicator did not know the group that each individual belonged to guarantee the masking character, minimizing the observer bias. The questionnaire was applied from July to December 2016 at each participant home. The average duration of the application of each questionnaire was 30 min. The study was previously authorized by all subjects who participated voluntarily, signing the informed consent form.^[26]

The inclusion criteria for this study were: People residing in the Águas Formosas microregion with the confirmatory diagnosis of ADs, of both sexes and aged from 7 years old, raised in any of the eight municipalities of the microregion. The inclusion of people from vulnerable/disabled groups was necessary since they constitute the majority of individuals diagnosed with type 1 diabetes mellitus (T1DM), due to the juvenile character of this condition.

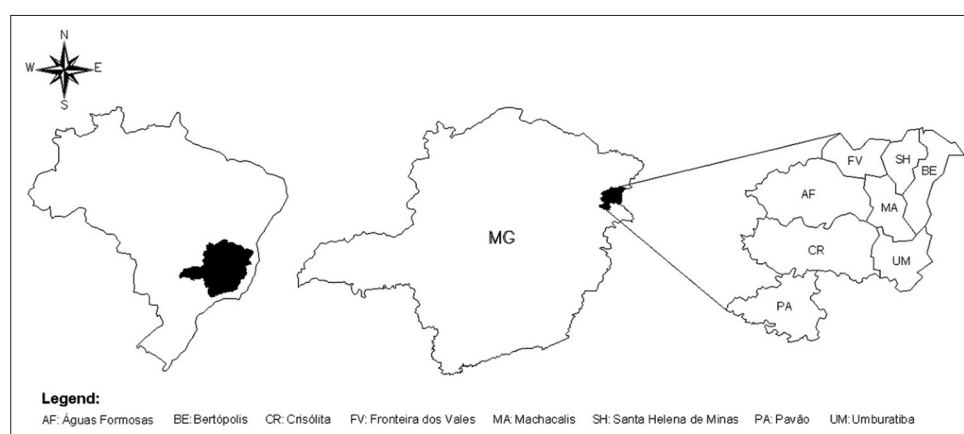


Figure 1: Map of the state of Minas Gerais and the Brazilian territory identifying the municipalities that comprise the Águas Formosas microregion

Participants were asked about their history of personal exposure to the following independent variables before the result of interest, such as: Have taken one to three doses of hepatitis B vaccine, having undergone at least one dental surgical procedure, having undergone at least one medical-surgical procedure, have suffered any physical and/or psychological trauma, have used hair dyes or other chemical agents by inhalation, have consumed filtered water with candles, have practiced physical exercise, (according to standards recommended by the World Health Organization), and have consumed cow milk before 6 months of age.

The elements considered for testing associations believed to be reliable, probable, or improbable for the identification of environmental and individual exposures associated with the predisposition and protection of the diseases in question were based on the Bradford Hill criteria,^[27] which are the strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy.

The case group was composed of 362 individuals of both sexes and aged between 7 and 60 years old or more; and the control group was formed with twice as many participants as the case group, strictly with the same sociodemographic profile, as shown in Table 1. The subjects in the case group that were considered for the study were 81 carriers of HT, 74 of vitiligo, 60 of RA, 36 of psoriasis (Pso), 33 of graves' disease (GD), 26 of SLE, and 20 of T1DM. The other 52 individuals with 17 different ADs were not statistically significant due to the reduced number of cases.

The control group consisted of 724 healthy individuals and was randomized by lot after individual matching by sex and age. For each case, 2 controls were drawn, selected within the same age group, gender, and geographic region, to obtain the highest possible similarity, avoiding confounding factors. Participant information was kept confidential following National Health Council Resolution 466/12, which complies with the Declaration of Helsinki.

Table 1: Pairing of variables according to sex and age between the related case and control groups

Variable	Cases (n=362)		Controls (n=724)	
	n	%	n	%
Sex				
Male	110	30.4	220	30.4
Female	252	69.6	504	69.6
Age group				
7-14	15	4.1	30	4.1
15-29	32	8.8	64	8.8
30-44	90	24.9	180	24.9
45-59	112	31.0	224	31.0
60 and over	113	31.2	226	31.2

The results were organized in tables with absolute numbers, and contingency column charts were prepared using GraphPad Prism 8 software^[28] and the discussion was descriptive. A case-control analysis was performed on the 7 most prevalent diseases matched for gender and age. The data collected were analyzed using BioEstat version 5.0 software.^[29] Categorical elements were described using simple logistic regression. Multiple logistic regression was used to estimate the odds ratio between the variables. Variables with $P < 0.05$ were significantly associated.

The study was approved by the Research Ethics Committee of the Federal University of the Jequitinhonha and Mucuri Valleys under registration CAAE 57185316.4.0000.5108.

Results

Distribution of ADs cases identified among the municipalities surveyed

Among the 24 cases of ADs identified by the medical archiving service of the primary health care units of the microregion, there was a higher concentration of cases in the municipality of Machacalis, followed by Umburatiba and Crisolita during the period evaluated [Figure 2].

Sociodemographic characteristics of 362 individuals who answered the questionnaire

In the sociodemographic analysis of individuals with ADs, there was a higher prevalence in women (69.6%), in working-age (64.7%), and brown-skinned people (77.1%), greater involvement in urban residents (81.8), in people with incomplete primary education (39.0%), and married individuals (53.3%), confirming that the different sociodemographic strata play an important role in the etiopathogenesis of ADs in this region [Table 2].

The sex ratio of 362 individuals with AD who answered the questionnaire

Table 3 shows an agreement between most of the diseases studied with other studies regarding the predominance of female cases, especially in those in which the literature indicated a female relationship superior to males.

Correlation of the seven most prevalent ADs with possible predisposing and protective factors

The most prevalent ADs were HT, GD, vitiligo, RA, Pso, T1DM, and SLE, accounting for 91% (330 subjects) of the case group sample [Table 4].

In these conditions, the behavioral variables: Having been vaccinated against hepatitis B, have undergone any surgical or dental procedure, have consumed cow milk in the first

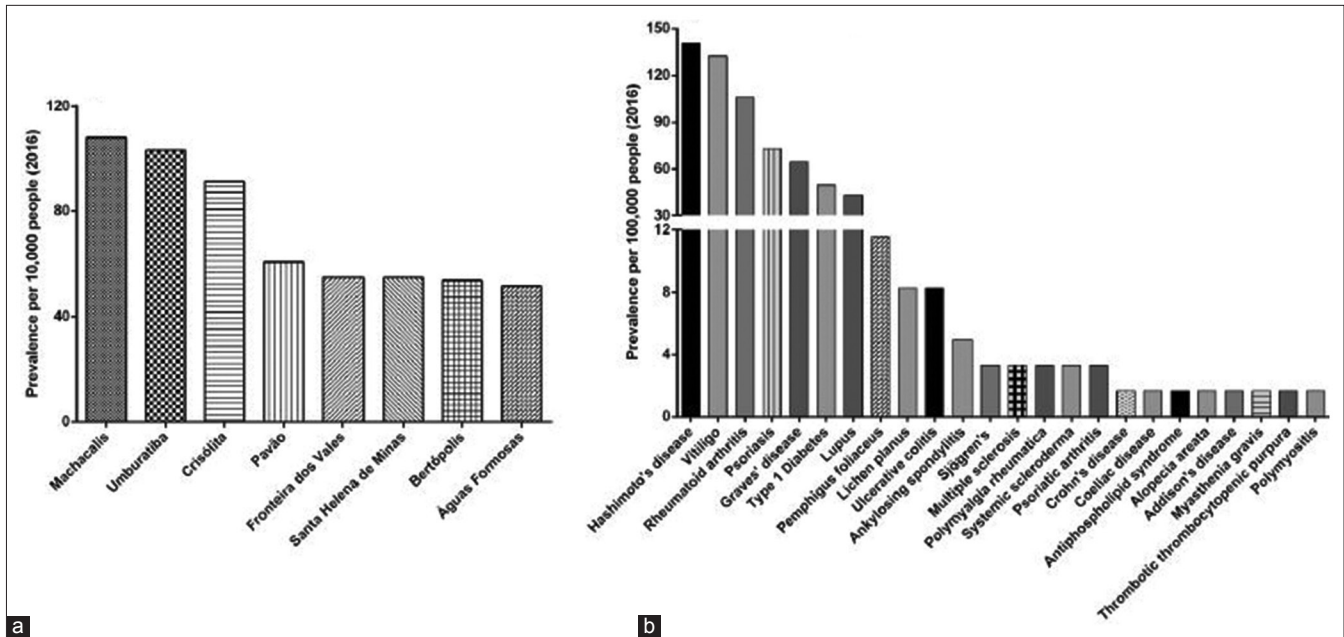


Figure 2: General prevalence of autoimmune diseases per 10,000 people, among the municipalities of the Águas Formosas microregion – Minas Gerais – Brazil, 2016 (a). Relative prevalence of the 24 autoimmune diseases identified in the microregion in 2016, per 100,000 people (b)

6 months of life, have used hair dye and chemicals, and having inhaled chemical solvents were considered predisponent factors, whereas have practiced physical activity and have consumed treated water were considered protective factors to the development of ADs.

Discussion

The research was carried out in the Águas Formosas Microregion, belonging to the Northeast Macroregion of Minas Gerais state, one of the most socially vulnerable regions in Brazil, known for its low social indicators and also for exhibiting characteristics of the Northeast region of Brazil, as a long drought period, high levels of poverty, malnutrition, mortality, illiteracy, unemployment, poor socioeconomic conditions, and political infrastructure.^[30] Comparing the general prevalence level among the evaluated municipalities, it is noted that Machacalis, Umburatiba, and Crisólita presented a higher concentration of cases [Figure 2]. There are no studies focused on this topic in the region, nor are current studies or data available for comparison of prevalence, government health agencies do not have specific public policies aimed at this group of diseases. When comparing the relative prevalence level of the present study with an Italian study,^[31] it is concluded that the microregion has a lower level probably because its municipalities have low demographic density and low latitude, in addition to the influence of socioeconomic factors advocated by the hygiene theory that argues that prevalence tends to be lower in less developed regions.^[32] Although research has shown an increasing trend in the incidence of rheumatological, endocrinological, gastrointestinal, and neurological ADs worldwide, including in Brazil.^[33]

Analyzing the data obtained in Table 2, it is possible to verify that this study found a higher prevalence of ADs in women, corroborating previous studies that stated that 78% of these conditions are more common in women.^[34-36] The high prevalence of brown and working-age individuals in the present sample is also corroborated by previous studies that show that AD affects all ethnicities and age groups.^[37] When assessing the origin of the sample, most came from urban areas, prevailing the group of people with incomplete primary education and married individuals, which confirms the thesis that sociodemographic factors are important because they act in the etiopathogenesis of these conditions.^[12]

Table 3 shows that the present study found a general the ratio of women/men of 2.3:1, with HT, SLE, and RA presenting a higher female proportion, corroborating with previous studies that state that women are 2.7 times more chances than men of acquiring an AD.^[36] Epidemiological studies have identified possible factors that explain the observed gender difference, such as fetal microchimerism, sex chromosome deletions, X chromosome gene inactivation, differences between male and female immune function, and different environmental factors.^[35]

Lockshin^[38] states that the expression of environmental factors acts equivalently between the sexes, and what varies are the circumstances of some factors such as infection, for example, attributed to different exposures and infectious agents, and the possibility of infections in periods of greater susceptibility, since microorganisms infect both sexes, causing equally the same sequelae in immunity.

Among the most accepted environmental factors for explaining susceptibility to HT are intrauterine factors associated with

Table 2: Sociodemographic characteristics of individuals with autoimmune diseases who were conducted with individual questionnaire application in the microrregion in 2016

Variable	n*	%
Cases	362	100
Sex		
Female	252	69.6
Male	110	30.4
Age		
7–14	15	4.1
15–29	32	8.8
30–44	90	24.9
45–59	112	31.0
60 and over	113	31.2
Ethnicity		
Black	17	4.7
Brown	269	77.1
White	66	18.2
Residence zone		
Urban area	296	81.8
Rural area	66	18.2
Educational level		
Unschooling	46	12.7
Incomplete primary education	141	39.0
Complete primary education	32	8.8
Incomplete high education	7	2.0
Complete high education	58	16.0
Incomplete higher education	5	1.3
Complete higher education	73	20.2
Marital status		
Single	110	30.4
Married	193	53.3
Divorced	28	7.7
Widower	31	8.6

*n: Number of cases

low fetal weight.^[39] Regarding vitiligo, nutritional deficiency, emotional stress, trauma, drugs, infections, sun exposure, and chemicals are recognized as the main triggers,^[40] smoking,^[41] and red meat intake are currently the main factors associated with RA.^[42]

Recent studies have shown that the vaccine against Hepatitis B would lead to ADs, especially RA.^[43] In the present study, it was observed that to patients with RA, GD, Pso, SLE, HT, and vitiligo, having been vaccinated against hepatitis B would tend to favor the onset of the disease [Table 4]. For this analysis, we consider the proof of one to three doses recorded on the vaccination certificate of the participants, considering that only one dose is sufficiently capable of generating an immunogenic effect. We proceed with due care to select only those cases in which the risk factor occurred at least 1 year before the observed disease.

Table 3: Relation of cases of different autoimmune diseases followed by questionnaire application, according to sex ratio

Autoimmune disease	Female cases	Male cases	Ratio F:M
Hashimoto's thyroiditis	73	8	7.1:1
Vitiligo	39	35	1.1:1
Rheumatoid arthritis	47	13	4.6:1
Psoriasis	21	15	1.4:1
Graves' disease	25	8	3.1:1
Type 1 diabetes mellitus	8	12	1:1,5
Systemic lupus erythematosus	22	4	5.5:1
Endemic pemphigus foliaceus	2	2	1:1
Idiopathic ulcerative colitis	2	2	1:1
Lichen planus	3	2	1,5:1
Ankylosing spondylitis	1	1	1:1
Sjögren's syndrome	2	0	2:0
Multiple sclerosis	0	2	0:2
Rheumatic polymyalgia	0	1	0:1
Scleroderma	2	0	2:0
Psoriatic arthritis	1	1	1:1
Crohn's disease	0	1	0:1
Celiac disease	0	1	0:1
Antiphospholipid syndrome	1	0	1:0
Alopecia areata	0	1	0:1
Addison's disease	1	0	1:0
Myasthenia gravis	0	1	0:1
Immune thrombocytopenic purpura	1	0	1:0
Polymyositis	1	0	1:0
Total	252	110	2,3:1

The hepatitis B virus vaccine is available to the entire Brazilian population, regardless of age or vulnerability. Newborns should receive the first dose (0.5 mL), preferably within the first 12 h of life. The continuity of the vaccination schedule is currently guaranteed with the application of the pentavalent vaccine in three doses, with an interval of 60 days between doses. For individuals from 5 years of age and without vaccination evidence, three doses of hepatitis B vaccine are administered, with an interval of 1 month (30 days) between the first and second dose and 6 months (180 days) between the first and third dose. At present, the cumulative hepatitis B vaccination coverage in the state of Minas Gerais is 56.1%, far from the goal of 95% to be achieved that is advocated by the Ministry of Health.^[44]

Thimerosal, which contains mercury in its composition, is added to the vaccine as a preservative to prevent microorganism contamination when formulated in multiple-dose vials. In mice, inorganic mercury causes polyclonal T-cell dependent B-cell activation, hypogammaglobulinemia, and production of autoantibodies against fibrillar.^[45,46]

Concerning the analysis of predisposing factors, it was observed that GD, vitiligo, Pso, and T1DM were related

Table 4: Association strength of the variables that predisposed or protected the development of autoimmune diseases in the sample obtained

Disease/variable	P*	Adjusted odds ratio	95% CI**
Grave's disease			
Have been vaccinated against hepatitis B	0.0004	11.9977	3.04–49.55
Have undergone a dental surgical procedure	0.0451	0.1728	0.02–0.96
Vitiligo			
Have had physical or psychological trauma	0.0074	5.9848	1.62–22.16
Have been vaccinated against hepatitis B	0.0001	10.2041	5.80–43.56
Have undergone a medical surgical procedure	0.0394	0.2848	0.09–0.94
Have undergone a dental surgical procedure	0.0025	0.2691	0.04–0.51
Have used hair dye or chemicals	0.0152	0.7142	0.11–0.79
Have consumed filtered water with candles	0.0009	0.3325	0.05–0.46
Have practiced physical exercises regularly	0.0152	0.4904	0.15–0.82
Rheumatoid arthritis			
Have been vaccinated against hepatitis B	0.0254	4.5422	1.94–14.31
Have consumed cow milk before 6 months of age	0.0156	0.2880	0.08–0.77
Have practiced physical exercises regularly	0.0006	0.2102	0.06–0.64
Have used hair dye or chemicals	0.0009	0.1405	0.04–0.62
Psoriasis			
Have been vaccinated against hepatitis B	0.0340	2.3509	1.11–13.47
Have consumed cow milk before 6 months of age	0.0494	0.3321	0.09–0.99
Have undergone a dental surgical procedure	0.0170	0.1592	0.02–0.69
Have practiced physical exercises regularly	0.0010	0.4050	0.09–0.72
Have undergone a medical surgical procedure	0.0415	0.2657	0.08–0.95
Have used hair dye or chemicals	0.0251	0.2779	0.06–0.83
Lupus			
Have been vaccinated against hepatitis B	0.0001	7.7518	4.41–35.00
Have practiced physical exercises regularly	0.0001	0.0047	0.06–0.37
Have inhaled chemical solvents	0.0483	0.2210	0.04–0.99
Hashimoto's thyroiditis			
Have been vaccinated against hepatitis B	0.0001	8.1969	4.41–35.00
Have practiced physical exercises regularly	0.0001	0.3133	0.06–0.37
Have inhaled chemical solvents	0.0043	0.2303	0.04–0.99
Type 1 diabetes mellitus			
Have undergone a medical surgical procedure	0.0209	0.0883	0.01–0.68
Have undergone a dental surgical procedure	0.0290	0.1160	0.01–0.78

*P: P-value; **CI: Confidence interval

to the fact that individuals had already performed dental surgery; toward the fact that other individuals performed general surgical procedures, there was an association with vitiligo, Pso, and T1DM. Many factors such as material sterilization failure, number of people in the operating room, and staff experience may be responsible for increasing the infection rate in underdeveloped countries such as Brazil.^[47] For these analyzes, it was considered dental surgical procedures as invasive interventions such as dental extractions, endodontics, implants, restorations, and dental reconstructions, and for general medical procedures, any surgical procedure from all medical clinics, except leisure surgery, was taken into account.

The participants in this study reported some signs of infection until the 2nd month after the invasive procedure. A recent study showed that 15% of those who developed Guillain-Barré syndrome underwent a surgical procedure 2 months before developing the disease after surgical procedures.^[48,49] Other studies have correlated bariatric surgery as a risk factor for the development of systemic ADs,^[50] and other research has associated autoimmune connective tissue disease as a result of abdominoplasty.^[51]

There are several recent reviews about the role of infections in the development of the ADs, and associations between infection and AD exacerbation.^[52] It is suggested that surgical

exeresis is related to phenomena of immune dysfunction, as the asepsis breakdown at any of the surgical times may concur with surgical site infections, and as is well known, infections may trigger loss of tolerance through various mechanisms. It is worth mentioning tissue damage and cell necrosis that expose cryptic epitopes present in autoantigens or allowing the access of immunocompetent cells to normally isolated antigens; polyclonal activation of T and B cells by microbial super antigens, such as toxins produced by *Staphylococcus aureus*; activation of immunocompetent cells not directly involved in the response of the pathogen, a condition called spectator activation and molecular mimicry.^[53]

When analyzing behavioral factors, studies have shown that protein intake of cow milk is associated with the progression of childhood T1DM and MS because this practice can produce unstable myelin by depriving different essential fatty acids, vitamins, and minerals in breast milk.^[54,55] Feeding infants with cow milk instead of mother milk can produce unstable myelin and predispose to MS because of deprivation of different essential fatty acids, vitamins, and minerals in breast milk.^[55] The findings showed that only RA and psoriasis were associated with this risky behavior that many Brazilian puerperal women practice for lack of experience and knowledge, despite the numerous governmental campaigns that encourage exclusive breastfeeding for at least 6 months of life.^[56]

A potential association between solvent exposure and increased risk of MS and SSc has also been investigated. Data on the possible role of chemical solvents in modulating other ADs are insufficient, with some studies reporting varying results for RA and SLE.^[57,58] Regarding the supposed behaviors that predispose the onset of ADs in people who were exposed to the previous contact with chemicals, it was observed that the cases of vitiligo, RA, and Pso were associated with hair dyes; on exposure to chemical inhalants, it was possible to identify that the cases of TH and SLE showed a causal link with this risky behavior. The use of permanent hair dyes in women was associated with a borderline increase in the risk of developing SLE, with a greater risk for those who used the product for a long time.^[59]

The first category referred only to the consumption of hair dyes and other chemicals used by people who usually go to beauty salons or self-apply these hair treatments. The second category referred to various situations tested, such as inhaling glue from shoemakers, exposure to pesticides, and veterinary products, in addition to certain occupational exposures experienced by hairdressers, manicurists, tinkers, painters, and gas station workers, who generally do not use personal protective equipment.^[60]

Evidence has indicated that products such as nail enamel are strongly associated with a primary biliary cirrhosis, as these halogenated compounds can bind to mitochondrial proteins, altering their immunogenicity and inducing anti-mitochondrial antibodies.^[61] In a study of 300,000 death certificates in 26

states of the United States over 14 years, researchers examined the association between occupation and death from AD. They found that rural workers working in fields where pesticides were used were more likely to die from an AD, including RA, SLE, and SSc.^[62]

The practice of physical activity has been effectively demonstrated in the control of different immune dysfunctions. Exercise stimulates the release of anti-inflammatory compounds such as cortisol and adrenaline and suppresses the release of pro-inflammatory cytokines.^[63-68] Different studies have found that the incidence of RA, MS, inflammatory bowel disease, SLE, and Pso is higher in sedentary patients.^[64] Furthermore, physically active carriers of RA had a milder course of the disease, improved joint mobility. Physical activity decreases fatigue, improves mood, cognitive skills and mobility in patients with MS. Lupus patients who are physically active have documented a better quality of life. Physically active patients with DM1 are at reduced risk of autonomic neuropathy. Patients with SSc, on the other hand, report a reduction in the severity of the disease and pain, improvement in grip strength, stretching of the fingers, and opening the mouth.^[63]

In the present study, physical exercise was a protective factor for the development of HT, Vitiligo, RA, Pso, and SLE. For this analysis, it was considered the World Health Organization recommended standard of at least 60 min of moderate to vigorous daily activity for children and youth aged 5–17 years,^[69] for adults aged 18–64, a minimum of 150 min of moderate-intensity aerobic physical activity during the week is recommended,^[70] for adults over the age of 64, at least 75 min of vigorous-intensity activities are recommended, including leisure activities (walking, dancing, swimming, and gardening), transportation activities (cycling), professional activities (household chores), games, play, and/or planned exercises in the context of daily family and community activities.^[71]

Concerning trauma caused by physical and psychological stress, such influence has been implicated in the development of ADs, since several studies in animals and humans have demonstrated the effect of various stressors on immune function.^[65] Besides, many retrospective studies have found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset. Recent reviews discuss the possible role of psychological stress and major stress-related hormones in the pathogenesis of the AD. Stress-triggered neuroendocrine hormones are presumed to lead to immune dysregulation, which results in ADs, altering or amplifying cytokine production.^[66]

It was observed that vitiligo was the only pathology among the collection that showed a relationship with traumatic factors. For the test of this hypothesis, it was considered psychological and physical trauma any significant life stressors before the illness, including loss of loved ones,

traumatic marital separations, and exposure to various types of disasters or violence. Individuals with these stress-related disorders undergo several physiological alterations, including disturbance of the hypothalamic-pituitary-adrenal axis^[65] and autonomic nervous system, which in turn may influence multiple body systems such as immune system function,^[67] developing susceptibility to the disease. About 8 of 10 people suffering from ADs experienced emotional stress before the onset of the disease.^[66]

Dental caries is the most prevalent infection in the world, and there is evidence that the development of certain ADs may be associated with the stimulation of dental plaque bacteria that induce antibody formation, self-reactive T cells, natural killer cells, anti-neutrophil cytoplasmic antibody, heat shock proteins, autoantibodies, and genetic factors that play an important role in the autoimmune component of periodontal disease.^[72-74] Regarding the challenge of drinking water treated as a protective factor against AD, only vitiligo was significantly associated. Considering that water quality is monitored weekly in municipalities evaluated with biological tests and that Brazilians consume ceramic water filters, capable of filtering pathogenic particles up to one micron, constituting an important public health measure by filtering parasites, pesticides, chlorine, and metals such as iron, lead, and aluminum.^[75]

Even with the recognition of the importance of water filtering for food consumption by most Brazilian consumers, a significant portion of the population still does not have a ceramic water filter or any other means of filtration, or not even has the work of at least boil it before consuming it, others usually consume it directly from the taps coming from the pipes, running risk own health damage due to the danger of microbiological contamination that the distribution system may cause due to the lack of preventive maintenance in its piping.

Considering this analysis, the fact that most respondents use the ceramic water filter at home and replace their candles at regular intervals of 6 months is a protective measure capable of containing most of the pathogens of waterborne transmission through the physical treatment employed, avoiding in many cases the breakdown of immunological tolerance induced by molecular mimicry in which the host cells confuse their constituents with pathogen proteins to which they had previously been in contact, thus modulating various autoimmune conditions.^[76,77] With a simple measure like this, it is possible to reduce the burden of these diseases because, according to studies consulted, microbial infections can also cause polyclonal activation of autoreactive lymphocytes.^[59] Biological mechanisms for the action of various infectious agents, especially periodontal infections, have been suggested for the etiopathogenesis of RA.^[78]

For the analysis of each proposed challenge, it was considered the minimum time interval of 1 year between each exposure

evaluated and the respective outcome (disease onset) so that there was no measurement and classification bias. The hypotheses presented significant associations with relative risks, which prove that the predisposing and protective factors tested are valid and that the chance cannot be ruled out as an explanation of some findings of this study.

The results of this study suggest that individuals with unfavorable socioeconomic conditions living in underdeveloped regions have higher immune tolerance and consequently lower risk of developing ADs, presumably because they have previously had contact with a wide range of pathogens, unlike populations in developed regions.

Despite this, the findings indicate that individual, environmental, behavioral, psychological, chemical, and biological factors tested in this region may predispose people susceptible to developing ADs. On the other hand, it is also suggested that behavioral and precaution can protect individuals from ADs, indicating a plausible relationship between cause and effect and their respective determinants and outcomes.

The current research is a reference for different underdeveloped regions of the world, as a way to motivate the conduct of new researches with a causality approach aimed at environments and risk behaviors for other ADs. Furthermore, it will be useful for health management to appropriate new perspectives of knowledge, control, and interventions that aim to contain the increased prevalence of these morbidities in the modern world.

Conclusion

ADs represent a major challenge for medicine worldwide due to its characteristic of a multifactorial, incurable disease and because it predominantly affects women and people of working age. Furthermore, the lack of studies focused on its etiopathogenesis, especially in less developed regions, puts at risk the possibility of a public policy aimed at controlling and intervening on its risk factors to reduce hospitalizations, disabilities, and deaths in this region.

Therefore, only employing crucial actions such as awareness among the most susceptible population to reduce the burden of risk factors and promote healthy lifestyles, investment in research in this area, and engagement between government, researchers, health professionals, and population it will be possible to overcome these conditions.

Author's Declaration Statements

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Federal University of the Jequitinhonha and Mucuri

Valleys (Approval Number CAAE 57185316.4.0000.5108). All participants signed written informed consent before they were involved in the study.

Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

Competing interests

The author declares no conflicts of interest.

Funding statement

Nothing to be declared.

Authors' Contributions

Dilceu S. Tolentino Júnior conducted the experiment and wrote manuscript, performed statistical analyses, revised the manuscript, designed the project, and provided participants' samples and medical information. The author revised the manuscript and read and approved the final version of the manuscript.

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