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Multifactorial Role of Carbon Dioxide in Autoimmune Diseases: From Membrane Depolarization to Gene Reprogramming

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ABSTRACT

Background: The incidence of autoimmune disorders has increased alongside rising carbon dioxide (CO_2) levels over the past century.

Objective: To determine whether elevated CO_2 levels are associated with autoimmune disorders.

Design: Case-control study conducted at local tertiary hospitals in Egypt.

Methods: A total of 150 patients diagnosed with various autoimmune disorders and 75 age- and sex-matched controls (aged 20–70 years) were enrolled. Exclusion criteria included neuromuscular disorders, critical illness, respiratory conditions, and occupational CO_2 exposure, as guided by criteria from the National Institute for Occupational Safety and Health. Recruitment occurred between November 2023 and March 2024. All participants underwent arterial blood gas analysis. Selected patients were further evaluated to confirm autoimmune status. Pa CO_2 was analyzed using two statistical methods to validate significance.

Results: The mean Pa CO_2 (± SD) was 48.18 ± 12.10 mmHg in autoimmune patients, compared to 42.63 ± 11.06 mmHg in controls (p = 0.001). Elevated Pa CO_2 was found in 97 (64.7%) of cases and 30 (40%) of controls, yielding a relative risk (RR) of 1.62. The odds ratio (OR) with 95% confidence interval (CI) was 2.75 (1.55–4.86), p = 0.0005.

Conclusion: Our study demonstrates a significant correlation between elevated CO_2 levels and autoimmune disorders. The underlying mechanism may involve complex interactions including CO_2-induced alterations in cell membrane integrity, calcium (Ca^{2+}) homeostasis, and intracellular signaling. The thermic effect of CO_2 may enhance antibody mobility away from their original antigens. Subsequently, CO_2 protonation increases

electrostatic interactions between anionic cell membranes and the positively charged antibodies, redirecting them toward host antigens and triggering autoimmune reactions. Tissues rich in negatively charged cells, such as skin and musculoskeletal tissues, are more affected. CO_2-driven changes in gene expression and mRNA translation may also contribute to diverse autoimmune phenotypes. This suggests a potential therapeutic role of targeting CO_2-related pathways. Based on these findings, a novel treatment approach for autoimmune disorders is proposed, involving membrane receptor modulation via CO_2-induced thermal oscillations of electron clouds, potentially leading to favorable phenotypic outcomes.

Keywords: Cell, Calcium, Autoimmune, CO_2, Ca^{2+}

INTRODUCTION

Background and Rationale: Despite the known effects of global warming on human health, no studies to date have specifically explored the cellular thermal damage caused by carbon dioxide (CO_2). In this study, we introduce a novel scientific concept based on the **thermo-acidotic impact** of CO_2 on individual cells and investigate how this may contribute to the development of autoimmune disorders. To the best of our knowledge, this is the first study to uncover a potential role for CO_2 in the pathogenesis of autoimmune diseases.

Objective. The objective of this study is to determine whether CO_2 is associated with autoimmune disorders.

CO_2 Properties and Biological Relevance. Carbon dioxide consists of one carbon atom and two oxygen atoms. It absorbs infrared radiation in a distinctive manner due to its vibrational stretching and bending patterns, which can amplify heat absorption. CO_2 is a key greenhouse gas, critical for terrestrial thermal regulation, and understanding its molecular absorption profile is vital for accurate climate simulations [1].

Biologically, CO_2 is acidic and transported in blood in several forms, primarily through the bicarbonate buffer system. Upon entering red blood cells, CO_2 is rapidly converted into carbonic acid by the enzyme carbonic anhydrase. This acid then dissociates into bicarbonate and hydrogen ions. Other forms of CO_2 are bound to hemoglobin as carbamino compounds [2,3]. Elevated levels of CO_2 in the blood—known as hypercapnia, defined as a partial pressure of CO_2 (Pa CO_2) above 45 mmHg—may arise in conditions such as sleep apnea and obesity, where respiratory retention of CO_2 overwhelms the buffering capacity of the blood [4].

Importantly, CO_2-induced heating from absorbed infrared energy can alter the electrical capacitance of plasma membranes, leading to depolarization and activation of thermosensitive ion channels that form pores in cell membranes [5]. These processes occur in conjunction with pH changes, as hydrogen ion concentration directly lowers the pH of bodily fluids [6].

Autoimmune Disorders. Autoimmune diseases represent a major and growing public health challenge. They occur when the immune system mistakenly attacks healthy tissues, leading to chronic inflammation, tissue damage, and organ dysfunction [7]. The root cause is typically a failure to eliminate or regulate self-reactive lymphocytes. Both genetic and environmental factors contribute to this failure [8].

Infections are well-documented triggers of autoimmune responses. They may initiate disease through mechanisms such as **molecular mimicry**, where foreign antigens resemble self-antigens, leading to a loss of peripheral tolerance. Other mechanisms include **defects in central tolerance**, **epitope spreading**, and **persistent antigenic stimulation** [9].

Autoimmune diseases emerge from the interplay of genetic predisposition and environmental exposure. Multiple genes involved in immune regulation may confer susceptibility. Notably, patients may produce autoantibodies long before clinical symptoms emerge—a stage referred to as **pre-clinical autoimmunity** [10].

Recent advances in immunology and molecular biology have led to **gene modulation** therapies targeting cytokine pathways. Techniques such as small interfering RNA (siRNA) can suppress pro-inflammatory cytokines like interleukins (ILs), tumor necrosis factor (TNF), CTLA-4, and interferon-γ. Other strategies involve delivering anti-inflammatory cytokines or their antagonists. These approaches have shown promise in

diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS) [11].

Calcium Channels and Homeostasis. Intracellular calcium (Ca^{2+}) signaling is tightly regulated by a network of channels, transporters, ATPases, and signaling effectors such as lipid kinases and phosphatases. Disruption of this regulation—particularly an excess of intracellular Ca^{2+}—can damage organelles like the endoplasmic reticulum (ER), lysosomes, and mitochondria [12].

The ER and sarcoplasmic reticulum (SR) serve as major calcium reservoirs within cells. Ca^{2+} channels, which include all pore-forming calcium-permeable proteins, mediate the release and uptake of calcium as part of intricate signaling cascades [13]. These Ca^{2+} signals encode biological information through variations in frequency, kinetics, amplitude, and spatial distribution [14]. Voltage-gated calcium channels are particularly important; they respond to changes in membrane potential and operate under electrochemical gradients. A key player is the **sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA)**, responsible for pumping Ca^{2+} back into the ER/SR after signaling events [15].

When ER/SR calcium stores are depleted, they are replenished via **store-operated calcium entry (SOCE)** mechanisms. The depletion is sensed by **stromal interaction molecules (STIMs)**, which then interact with **Orai1** proteins to form **calcium release-activated calcium (CRAC)** channels [16]. STIMs are sensitive not only to calcium depletion but also to temperature increases and acidosis—conditions influenced by elevated CO_2. They can also regulate other proteins, including voltage-operated CaV1.2 channels, TRPC channels, and SERCA pumps [17]. Altered calcium homeostasis in lymphocytes has been implicated in both autoimmune and immunodeficiency syndromes, underscoring the immunological relevance of calcium regulation [18].

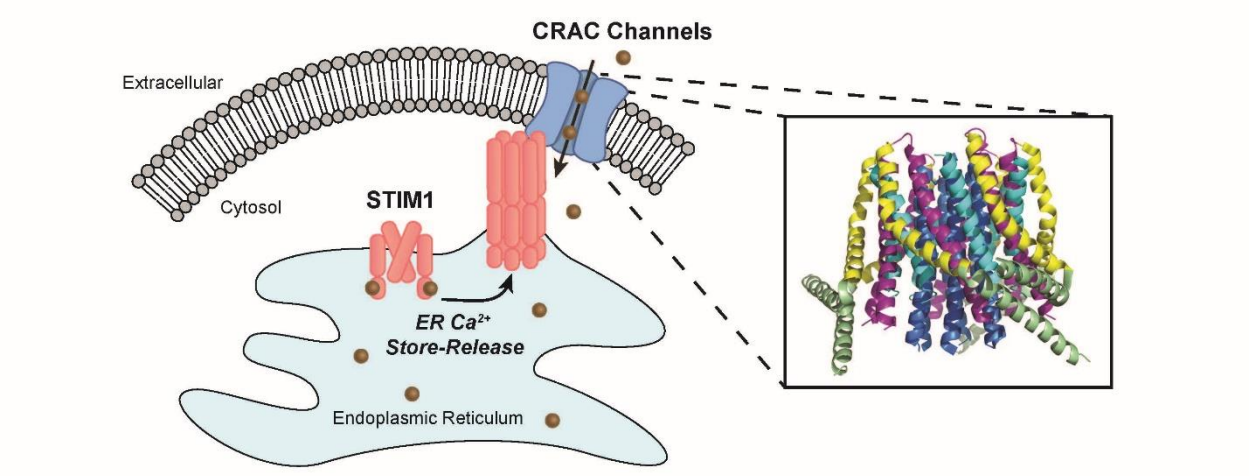


Figure 1. Diagrammatic Representation of "Orai1 protein" receptors known as Calcium-Release Activated Channels (CRAC).

Direct blockade of the calcium channel pore can occur from the extracellular side by peptide toxins such as **conotoxin GVIA**, or from the cytoplasmic side by small molecules. These blockers target regions within the ion-conducting pathway and inhibit ion permeation through the channel (black arrows = pore blockers) [19].

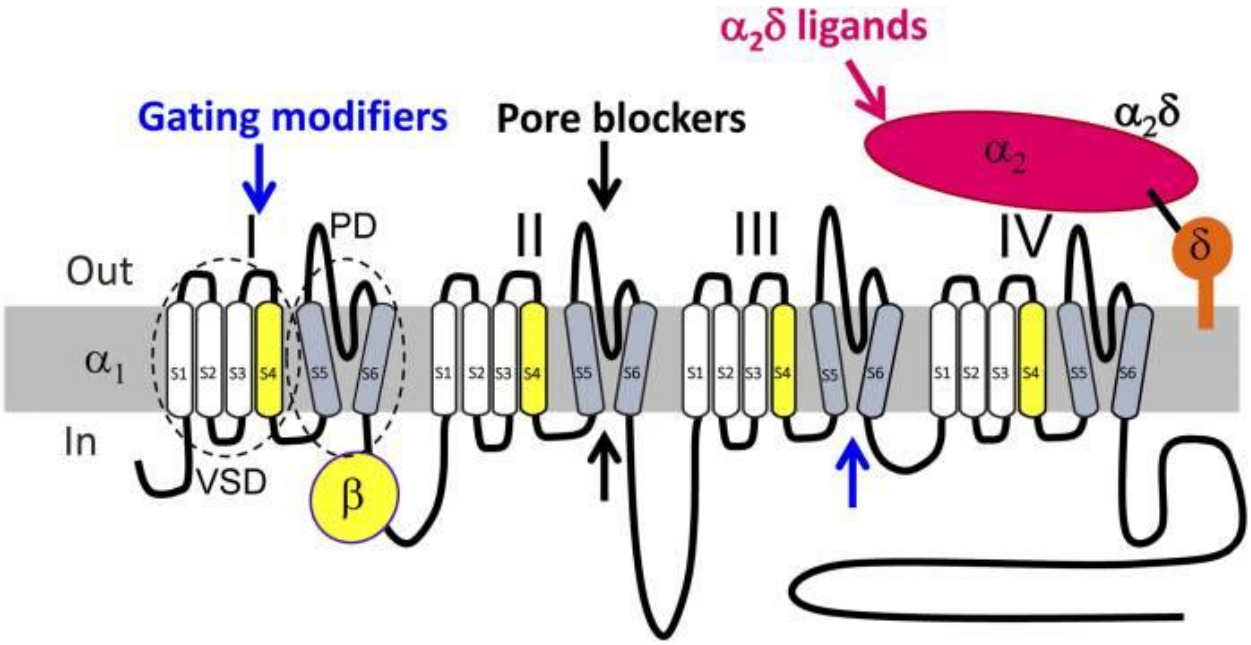


Figure 2. Voltage-gated calcium channel subunit topology showing major drug binding mechanisms. Channel inhibition can be induced by modification of channel gating (blue arrows, gating modifiers) by interaction with extracellular regions within one or more of the four voltage-sensing domains (VSDs) or within the activation gates of the pore domain (PD) channel, formed by all four S5–S6 helices together. Direct block of the pore from the extracellular side (by peptide toxins conotoxin GVIA) or small molecules (with access from the cytoplasmic side) can also target regions within the ion conducting pathway and obstruct permeation through the pore (black arrows = pore blockers). [19].

Calcium channels also generate spatially localized signaling events. These can manifest as elementary calcium signals known as "puffs" or "sparks," and often involve organized complexes formed with proteins such as G-protein–coupled receptors or receptor tyrosine kinases [20].

Acidic environments have been shown to suppress anti-tumor T lymphocyte function, partly by significantly upregulating inhibitory immune checkpoints such as **TIM-3**, **LAG-3**, and **CTLA-4** on T cells [21]. This acidosis-induced immune checkpoint upregulation contributes to immune evasion and tumor progression. Moreover, extra tumoral acidity has been implicated as a mechanism of resistance to CTLA-4 inhibitors [22,23]. CTLA-4 plays a pivotal role as a negative regulator of autoimmune responses [24]. Importantly, the functional integrity of the **CD28** molecule is required for the manifestation of autoimmune disease in **CTLA-4** knockout models [25].

Calcium (Ca^{2+}) is a vital second messenger in various immune cells. Disruption of intracellular Ca^{2+} signaling pathways has been linked to the pathogenesis of both autoimmune and congenital immunodeficiency syndromes [26]. Dysregulated Ca^{2+} signaling is a key contributor to the progression of autoimmune diseases [27].

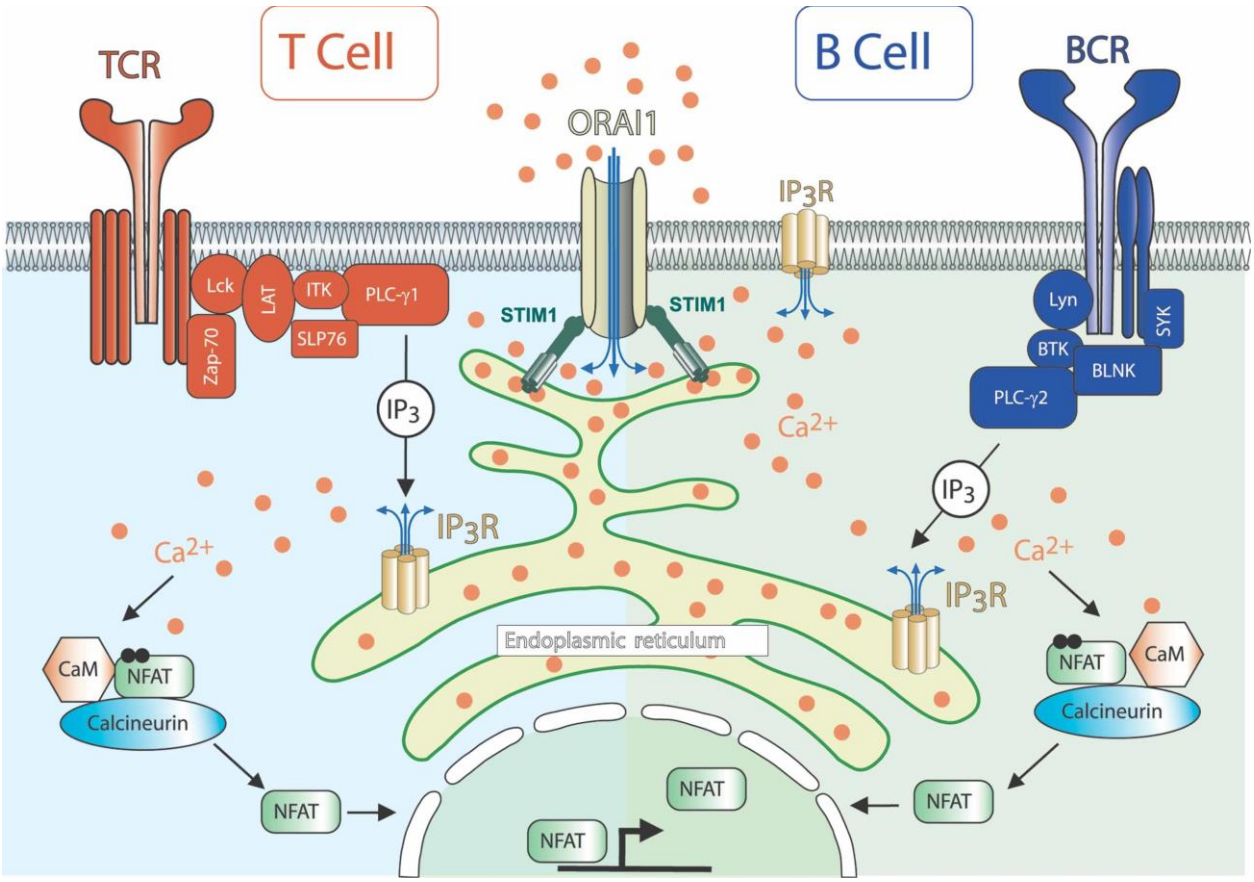


Figure 3. illustrates the **calcium–calcineurin–nuclear factor of activated T cells (NFAT)** signaling pathway as a novel therapeutic target. **Orai1** is a plasma membrane protein with four transmembrane segments, while **STIM1** is a single-pass transmembrane protein located in the endoplasmic reticulum (ER). When intracellular Ca^{2+} levels rise due to Ca^{2+} influx through calcium release–activated calcium (CRAC) channels mediated by Orai1, this activates the phosphatase **calcineurin**. Activated calcineurin then dephosphorylates several serine residues on NFAT, enabling NFAT to translocate into the nucleus. Once in the nucleus, NFAT binds to DNA and regulates gene expression. Given that dysregulated Ca^{2+} signaling contributes to autoimmune disease pathogenesis, targeting store-operated Ca^{2+} entry (SOCE) through the **Orai1–STIM1** pathway presents a promising therapeutic strategy for autoimmune disease control [27].

METHODS

To our knowledge, this is the first study to uncover the potential role of carbon dioxide (CO_2) in the pathogenesis of autoimmune disorders. It is important to note that, due to the presence of extraneous variables not fully controlled for in this design, the findings suggest a possible association but cannot establish causality.

Assessment of arterial partial pressure of CO_2 (Pa CO_2) has been the gold standard for many decades. These data are important not only in clinical diagnostics but also in the context of climate change and indoor air quality regulation, especially for ensuring adequate ventilation. Measurements of CO_2 production relative to oxygen consumption yield important indices such as estimates of energy expenditure, which may be used in further research in fields like metabolism, autoimmune disorders, obesity, and lifestyle-related conditions [28]. To control for confounding variables, we adopted strict exclusion criteria and incorporated CO_2 exposure into the study design and examination parameters.

Study Design. This was a case–control study, where participants were selected based on established matching criteria from prior knowledge of associations with autoimmune outcomes.

Setting & Participants. The study was approved by the administration of Hurghada, Marsa Alam, and Nasser Institute Hospitals in Cairo, Egypt. Routine consent for laboratory testing was obtained in accordance with hospital protocols, and the study adhered to the ethical principles of the 1975 Declaration of Helsinki.

Variables. Cases and controls were matched for potential confounders and recruited from the same geographic and population background. Selected demographic and clinical parameters—including age, sex, urbanization status, socioeconomic status, and comorbidities—were closely balanced between the two groups. All participants underwent physical examinations, including measurement of vital signs, weight, height, and body mass index (BMI). Demographic and health-related data were collected using a questionnaire that included items on age, sex, occupation, smoking status, family history, chronic respiratory illness, and occupational exposure to CO_2—assessed based on criteria from the National Institute for Occupational Safety and Health (August 1976). Special care was taken to exclude individuals working in agriculture, mining, or industries involving significant CO_2 exposure.

Data Sources / Measurement. Cases were identified through patient rosters at participating hospitals. The comparison group (controls) was representative of the source population that produced the cases and was sampled independently of autoimmune exposure. Both groups were matched for sociodemographic characteristics. Eligible cases were enrolled from both outpatient clinics and inpatient admissions after obtaining informed consent. The study was approved by the respective medical ethics review boards. Printed medical records were used to verify inclusion criteria, administered treatments, clinical assessments, family and past medical history, and laboratory test results.

Participants underwent arterial blood gas testing using the **ABL90 FLEX PLUS** blood gas analyzer to determine Pa CO_2. Participants were stratified based on whether their Pa CO_2 was above or below the median value. The standard reference range for Pa CO_2 was 35–45 mmHg.

Sample Size & Bias. Participants were recruited between November 2023 and March 2024, to account for the known seasonal variation in autoimmune disease incidence [29]. A total of 150 cases (77 males and 73 females) with various autoimmune disorders were compared to 75 controls (40 males and 35 females), all aged between 20 and 70 years. The unequal group sizes do not affect the validity of results, as case–control studies rely primarily on the relative frequency of exposure in each group (i.e., event occurrence and association strength), not absolute equality of numbers.

Although this study focused on CO_2 and Ca^{2+} effects, future rigorous investigations should evaluate additional factors such as vitamin D. Pa CO_2 data were analyzed using two statistical approaches to validate the results: (1) percentage of event occurrence and (2) the mean and standard deviation of Pa CO_2 values.

Quantitative Variables. Participants were free of any diseases known to affect Pa CO_2, such as cardiopulmonary disorders, neuromuscular conditions, critical illnesses, or multisystem organ failure. When necessary, confirmatory testing was performed to validate the diagnosis of autoimmune disorders.

Statistical Analysis. All analyses were conducted using **SPSS, version 18.0** (SPSS Inc., Armonk, NY, USA). Demographic characteristics between cases and controls were compared using **Fisher's exact test**, with calculations of **adjusted Odds Ratios (ORs)** and **95% Confidence Intervals (CIs)**.

RESULTS

This study was designed to investigate the association between elevated carbon dioxide (CO_2) and calcium ion (Ca^{2+}) levels and the incidence of autoimmune disorders.

Participants. A total of 150 patients with various autoimmune disorders and 75 matched controls were included. The findings, derived from matched data, indicate a strong association between elevated Pa CO_2 levels and an increased incidence of autoimmune disorders.

Descriptive Data.
(Table 1) summarizes the distribution of autoimmune diseases among the cases. Participants were carefully screened to exclude underlying cardiovascular or pulmonary conditions that could predispose them to elevated CO_2 levels. Table 2 presents the demographic characteristics and examination parameters of both cases and controls. Table 3 explores the association between obesity, overweight and case status. Table 4 provides an analysis of arterial partial pressure of CO_2 (Pa CO_2) across the two groups. Pa CO_2 was analyzed using two

statistical approaches: (1) the percentage of elevated events, and (2) the comparison of mean ± standard deviation (SD). Figure 1 graphically illustrates these Pa CO_2 findings.

Table 1. Distribution of Autoimmune Diseases Among Cases
Total cases = 150 (Males: 60, Females: 90)

Case category	Number of cases, n (%)	Male / Female, (60/90)
RA (Rheumatoid Arthritis)	40 (26.7)	18 / 22
SLE (Systemic Lupus Erythematosus)	30 (20)	5 / 25
JDM (Juvenile Diabetes Mellitus)	24 (16)	11 / 13
IBD (Inflammatory Bowel Disease)	18 (12)	9 / 9
Celiac Disease	14 (9.3)	6 / 8
Vitiligo	9 (6)	5 / 4
Psoriasis	9 (6)	4 / 5
EGACU (Extra gastric Autoimmune Chronic Urticaria)	6 (4)	2 / 4

Abbreviations: RA = Rheumatoid Arthritis, SLE = Systemic Lupus Erythematosus, JDM = Juvenile Diabetes Mellitus, IBD = Inflammatory Bowel Disease, EGACU = Extragastric Autoimmune Chronic Urticaria.
RA= rheumatoid arthritis, SLE= Systemic lupus erythematosus, JDM= Juvenile diabetes mellitus, IBD= Inflammatory bowel diseases, EGACU= Extra gastric Autoimmune Chronic Urticaria.

Table 2. Demographic characteristics and clinical parameters.

Variable	Cases (n = 150), n (%) or Mean ± SD	Controls (n = 75), n (%) or Mean ± SD	Odds Ratio (95% CI) Statistical Details	P-value
Sex (Male)	60 (40%)	32 (42.7%)	OR = 0.90 (0.511, 1.572)	0.3507
Age (years)	47.9 ± 14.5	50.1 ± 13.4	95% CI: –1.742 to 6.142; SE = 2.00	0.273
BMI (kg/m²)	27.6 ± 5.1	26.1 ± 5.3	95% CI: –2.94 to –0.06; SE = 0.73	0.0413
Current Smokers	34 (22.7%)	12 (16%)	OR = 1.54 (0.744, 3.181)	0.1223

Total annual outcome, (USD)	Cases	Controls.
≤ 12000.	87 (58%)	44 (58.7%)
12000 – 30000	47 (31.3%)	24 (32%)
≥ 30000	16 (10.7%)	7 (9.3%)

Table 3. Association of Obesity and Overweight with Case Status.

BMI Category	Cases N (%)	Controls N (%)	Odds Ratio (95% CI)	P-value
Obesity (BMI ≥30)	18 (12.0%)	3 (4.0%)	3.27 (0.93–11.46)	0.049
Overweight (BMI 25–29.9)	19 (12.7%)	5 (6.7%)	2.03 (0.73–5.67)	0.15

Note: P-values were derived from Fisher's exact test due to small, expected cell counts. The data suggests a **potentially meaningful association between obesity and the disease/condition being studied**, with borderline statistical significance. The association with overweight status is **not statistically significant**, possibly due to sample size limitations or a genuinely weaker effect. Further studies with larger sample sizes are recommended to confirm these associations and better define risk gradients across BMI categories.

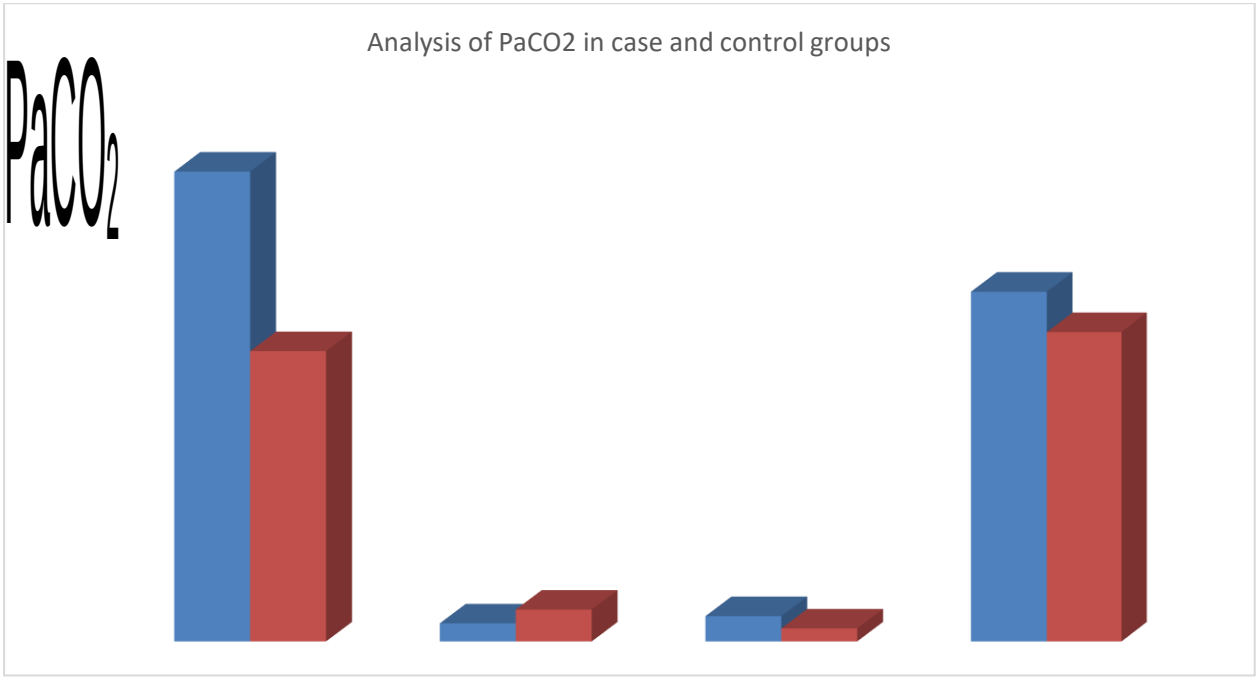
Table 4. Pa CO_2 analysis among cases and controls.

Parameter	**Cases**	**Controls**	**95% CI**	**SE**	**P-value**
Pa CO_2 (Mean ± SD, mmHg)	48.18 ± 12.10	42.63 ± 11.06	–8.83 to –2.27	1.66	0.001 **
No. (%) with ↑ Pa CO_2	97 (64.7%)	30 (40%)	OR = 2.75 (1.55, 4.86)	—	0.0005 **
Relative Risk (RR)	—	—	RR = 1.62	—	—

Pa CO_2 = partial arterial pressure of carbon dioxide; SD = standard deviation; OR = Odds Ratio; CI = Confidence Interval; SE = Standard Error.

To better illustrate these findings, Pa CO_2 was analyzed using two statistical approaches: (1) the percentage of elevated values and (2) the mean ± standard deviation (SD). Both methods consistently demonstrated a significant association between higher Pa CO_2 levels and the prevalence of autoimmune diseases.

To minimize potential confounding variables related to examination parameters, CO_2 exposure was evaluated based on predefined exclusion criteria. Pa CO_2 was intentionally analyzed through the two statistical methods to further clarify this association.



. **Participants**

Figure.4. Blue bars represent cases; brown bars represent controls. The left panel displays the percentage of participants with elevated Pa CO_2; the right panel shows the mean Pa CO_2 values in each group.

DISCUSSION

Key Results. The world is currently undergoing a profound and unprecedented transformation due to climate change. The unique properties of carbon dioxide extend from cellular effects—altering electric potential, acidity, and homeostasis—to a broader impact on planetary warming. Advances in the understanding of Ca^{2+} signaling in immune regulation, alongside the rising incidence of autoimmune diseases, prompted our investigation into a potential link between CO_2 and autoimmunity. We propose a mechanistic framework connecting CO_2, Ca^{2+}, calcium channels, second messengers, and autoimmune disease pathogenesis.

This hypothesis is reinforced by the discovery of a precise relationship between CO_2 and Ca^{2+}, and by emerging evidence that Ca^{2+} signaling encodes information via frequency, kinetics, amplitude, and spatial dynamics. These signaling properties influence cellular communication at multiple levels—receptors, cytokines, interleukins, genes, and mRNA expression. Our findings suggest that CO_2 can initiate, sustain, and stabilize autoimmune responses.

Strikingly, CO_2 illustrates the complex and multifactorial relationship between environmental factors and autoimmunity. This study presents mechanistic insight into CO_2-mediated autoimmunity and introduces the concept of an "intracellular binding role" for thermally and acidotically active CO_2. It also emphasizes the role of Ca^{2+} channel dynamics and signaling "sparks" in disease progression. Exploring the coordinated interplay between CO_2 and Ca^{2+} provides a foundation for deeper understanding of cellular responses to thermally altered proteins.

Though complex, this emerging concept appears mechanistically coherent and functionally integrated. Both CO_2 and Ca^{2+} serve as subcellular second messengers, with CO_2 exerting thermo-acidotic effects on all cells, and Ca^{2+} channels playing essential roles in various physiological processes. Special calcium-sensing proteins, such as STIMs, respond not only to Ca^{2+} depletion but also to thermal and pH stress. Park et al. reported that Orai1 mutations in autoimmunity reduce cytokine expression (e.g., IL-1, IL-4, IL-17, IFNγ, TNF-α) in $CD4^+$ and $CD8^+$ T cells [27]. Soboloff et al. showed that STIMs regulate proteins beyond Orai channels, including voltage-operated channels, plasma membrane Ca^{2+}-ATPase, and SERCA Ca^{2+} pumps [17]. Using this approach, we examined molecular protein receptors and channels in living cells, providing unprecedented insight into the sequence of events mediating stress-induced autoimmune disorders. Our study presents the first direct evidence linking CO_2 exposure with autoimmune disease. Notably, elevated arterial PCO_2 may represent a primary pathogenic mechanism. This involves a dynamic interplay between local effects of CO_2 on membrane and cellular homeostasis and Ca^{2+}-dependent signaling pathways.

Phelan [30] suggested that CO_2 acts as a central signaling hub in gene transcription and cytokine regulation. By re-emitting infrared radiation, CO_2 induces rapid increases in intracellular temperature and electrostatic excitability. Ahamad et al. [31] demonstrated that Ca^{2+} entry activates nuclear factor NF-κB translocation, initiating transcriptional programs linked to immune function.

Contrary to the long-held belief that CO_2 crosses membranes solely by passive diffusion, we introduce the novel concept of CO_2's "drill-like" entry via dedicated channels or membrane disruption, facilitating Ca^{2+} influx against its gradient. This enhances the secondary messenger cascade initiated by CO_2's rapid entry.

At the cellular level, Mistrik et al. reported that thermal damage disrupts protein folding, causing denaturation and aggregation [32]. Nadal et al. noted that adaptive responses to thermal stress involve substantial gene expression reprogramming, depending on the severity of micro-thermal damage [33].

This study reveals a significant statistical association between elevated arterial carbon dioxide (CO_2) levels and autoimmune disorders. The results indicate that CO_2 plays a pathogenic role by disrupting cell membrane structure, intracellular calcium (Ca^{2+}) homeostasis, and the immune signaling network—collectively contributing to the development of autoimmunity.

These findings align with previous reports of rising autoimmune disease incidence over recent decades [1], a period that has also seen increased global CO_2 emissions and atmospheric retention [2,3]. The thermal and chemical properties of CO_2 suggest its ability to modify cellular microenvironments, particularly by altering membrane polarity and ion gradients.

CO_2 has been shown to modulate cell membrane properties directly through its influence on lipid bilayer polarity and protein charge distribution [4-6]. Due to its thermodynamic characteristics—including high diffusivity, low surface tension, and high heat capacity—CO_2 can alter membrane orientation and fluidity. These alterations depolarize the plasma membrane and activate voltage-gated Ca^{2+} channels, leading to increased cytosolic Ca^{2+} levels and the initiation of signaling cascades that affect gene expression, immune cell function, and tissue homeostasis [7-9].

CO_2's impact is further amplified through its interaction with intracellular buffering systems. By lowering pH, CO_2 changes the protonation state of amino acids—particularly histidine—within membrane proteins, cytoskeletal structures, and transcription factors. Protonation of histidine induces ionization of the imidazole ring, modulating protein conformation and enhancing signal propagation via G-proteins and other second messenger systems [10-13]. This mechanism may contribute to aberrant immune activation and loss of tolerance, consistent with elevated Pa CO_2 levels observed in autoimmune patients.

Furthermore, our study suggests that CO_2 facilitates autoimmunity through antibody misdirection. The thermal properties of CO_2 may increase antibody mobility, allowing displacement from their original antigens. Once dislocated, these antibodies may interact with negatively charged host tissues. Elevated proton concentrations enhance electrostatic interactions between positively charged antibody regions and anionic cell membrane surfaces—particularly in tissues such as the joints, skin, and gastrointestinal tract, which are rich in negatively charged phospholipids and glycoproteins [14,15]. The specific involvement of cartilage, ligaments, and skin in autoimmune injury may be explained by their high content of anionic components and susceptibility to mechanical stress, which increases membrane vulnerability. This is consistent with clinical patterns seen in rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and vitiligo [16-19].

We also propose a novel hypothesis involving a "drill-like" mechanism by which CO_2 penetrates the cell membrane. This may occur via specific channels or by inducing membrane curvature, leading to localized heating and ion fluxes—particularly of Ca^{2+} [20,21]. Once inside the cell, CO_2 may influence mitochondrial function, endoplasmic reticulum stress responses, and intracellular calcium stores, contributing to long-term immune dysregulation.

At the gene expression level, CO_2 and Ca^{2+} may act synergistically to alter chromatin accessibility and transcription factor activity. These changes may affect histone acetylation and methylation, resulting in epigenetic reprogramming of immune cells [22-24]. Such mechanisms could account for phenotypic heterogeneity among patients with similar genotypes but varying levels of environmental CO_2 exposure.

Our findings also suggest that CO_2 affects the stability of antigen-antibody complexes. High CO_2 levels may destabilize these interactions by inducing conformational shifts and altering local charge distribution, thereby reducing antibody specificity and increasing cross-reactivity with host tissues—key features of autoimmune pathology [25-27].

Additionally, T-cell receptor (TCR) binding to major histocompatibility complex (MHC) molecules is highly sensitive to membrane dynamics and ionic environments. CO_2-induced changes in membrane fluidity and temperature may disrupt TCR–MHC orientation, thereby promoting autoreactive T-cell activation [28,29]. Notably, CO_2 appears to override normal immune homeostasis by enhancing calcium influx and modifying gene transcription. Previous studies have shown that CO_2 acts as a biological regulator influencing cytokine secretion and immune cell activation [30-32]. These effects may be exacerbated in genetically predisposed individuals or under environmental stressors such as vitamin D deficiency or infection [33-35].

In summary, our results elucidate a novel, multi-step mechanism by which elevated CO_2 levels contribute to autoimmune disease initiation and progression, involving:

1. CO_2-induced membrane depolarization and Ca^{2+} influx.

2. Protonation of histidine and activation of intracellular signaling.

3. CO_2 facilitates autoimmunity through the displacement with aberrant localization

of antibodies and cross-reactivity of antibodies.

4. Thermally mediated instability of antigen-antibody complexes.

5. Disruption of TCR–MHC complex orientation.

6. Transcriptional reprogramming through epigenetic modification.

These findings redefine CO_2 as a regulator of immune function with direct relevance to autoimmune disease, beyond its role as a metabolic byproduct or pollutant.

Heating reversibly alters the electrical capacitance of plasma membranes, depolarizing target cells, triggering thermosensitive ion channels, ultimately forming membrane pores, and increasing conductance, which activates intracellular second messengers. Tsai et al. assessed the role of infrared-stimulated transmembrane ion channels in generating selective, rechargeable electrolytic bio-batteries. These involve pathways including Ca^{2+}, ATP, and GTP, which provide energy for cellular functions such as signaling and gene transcription [34].

Our findings demonstrate that CO_2 imposes an acidic microenvironment that plays a critical role in regulating signaling cascades and Ca^{2+}-dependent transcription factors. These factors modulate gene activity via three principal pathways that ultimately culminate in autoimmune activation. CO_2 diffuses freely across cell membranes, sustaining intracellular acidity. Thiel et al. [35] have delineated these pathways in detail. To adapt to environmental changes, cells must regulate gene expression, a process in which intracellular Ca^{2+} serves as a key mediator linking surface events to nuclear responses. It is evident that CO_2's effects on immune cell function depend on both pH alterations and CO_2-sensing mechanisms involving ion channels that generate action potentials.

Similarly, the intracytoplasmic Ca^{2+}-mediated mechanism in autoimmune disorders appears pivotal for activating cytokine pathways and transcription factors central to autoimmune pathogenesis. This occurs through a communication network involving ion channels, transcription factors, and gene regulatory elements. Thiel et al. and Yeh et al. support this concept [35,36]. Given that CO_2 influences immune gene expression and Ca^{2+} influx activates key transcription factors such as NFAT, NF-κB, and c-Fos, these factors collectively orchestrate cytokine production and immune tolerance [26,34]. Guo et al. demonstrated that oscillatory NF-κB activation promotes inflammatory gene transcription, whereas persistent activation reprograms the epigenome to engage broader gene networks [37].

In studies evaluating the effect of acidity on immune cell function, cell type, receptor expression, and downstream responses must be considered. The connection between acidity-induced stress signaling and immune suppression aligns with Davern's findings, which showed that low pH significantly impairs anti-tumor T lymphocyte activity through upregulation of immune checkpoint molecule CTLA-4 [21]. Navarro and Sun further reported that immune checkpoint blockade (ICB) targeting these acidity-induced molecules may be necessary to overcome treatment resistance [22,24]. These findings suggest that acidosis-induced upregulation of immune checkpoints such as CTLA-4 may contribute to immune evasion and promote the development of autoreactive T-cells by skewing the balance between effector and regulatory T cells [25,38]. Consistent with Peter et al. [39], who highlighted the protective roles of CTLA-4 and PD-1/PD-L1 against autoimmune myocarditis, we conclude that CO_2 contributes to autoimmune pathogenesis. This conclusion is supported by studies from Guo et al. and Hossen et al., which underscore CTLA-4's role as a key negative regulator of T cell activation and autoimmunity [37,38].

T cells play a central role in maintaining immune homeostasis. Their activation is tightly regulated by microenvironmental signals and signaling pathways. In this context, CO_2 may activate signaling cascades and transcriptional programs that push autoreactive T cells toward sustained activation and autoimmune progression. This may be driven by CO_2 alone or by a combined CO_2-Ca^{2+} circuit. Differential gene expression observed in autoimmune disease could reflect compensatory responses to inflammatory stress. In support, Casalino et al. reported that hypercapnia (elevated CO_2) downregulated 183 genes, including several involved in immune responses [40].

We further propose that the acidic environment induced by CO_2 leads to protonation of histidine residues, ionization of imidazole rings, and conformational changes that activate heterotrimeric G-proteins, increasing intracellular second messengers such as cAMP [41]. Our study on autoimmune cases suggests that CO_2 exerts its effects via multiple pathways: direct action, Ca^{2+}-induced pathways, and downstream effects on immune regulation. Data from Marchesan et al. further support our conclusions [42].

Importantly, CO_2 plays a physiological role in maintaining cellular pH via the CO_2-bicarbonate buffer system and helps stabilize temperature in cell culture environments [43]. These conditions facilitate cellular functions, including intracellular Ca^{2+} elevation and activation of transcription factors, receptors, and ion channels.

Summary of CO_2 and Autoimmunity Induction. CO_2 not only initiates but also sustains autoimmune processes, explaining why autoantibodies often appear long before clinical symptoms. Our study also explored how CO_2 influences antigen-antibody (Ag-Ab) interactions. CO_2's chemical reflex underpins electrostatic bonding between epitopes and paratopes, promoting antibody interactions and molecular complementarity. Quantum mechanical principles explain that chemical bonds, including those between antigens and antibodies, are based on electrostatic forces and are temperature sensitive. High temperatures reduce binding affinity, while low temperatures stabilize Ag-Ab complexes. For instance, antigen–antibody dissociation typically requires heating to 56°C [44]. Moreover, the elevated temperatures associated with CO_2 generally lower the pH of aqueous solutions by promoting water autoionization and shifting acid-base equilibria, in accordance with Le Chatelier's principle—a trend well-documented in both theoretical and empirical studies [45].

B cells neutralize pathogens by targeting them with membrane-bound receptors, relying on molecular complementarity between the paratope and the epitope [46]. These epitopes, found on pathogens or host cells, trigger the production of antibodies, which bind with high affinity through hydrogen bonds and electrostatic interactions. Akbar et al. [47] showed that common structural motifs in epitopes and paratopes predict binding affinity. The strength of this interaction is influenced by geometric fit, reaction time, temperature, pH, and ionic strength. Low ionic strength enhances Ag-Ab sensitivity [44,49]. Local acidity can disrupt these interactions by weakening hydrogen and electrostatic bonds, altering antibody structure, and reducing efficacy. Acidic endosomal pH also impairs antigen recycling and promotes lysosomal degradation [50]. Hironiwa showed that Ca^{2+}-dependent antibody-antigen interactions dissociate more efficiently in acidic environments, accelerating antigen clearance [51].

CO_2 and Epitope-Paratope Interactions. CO_2 impairs Ag-Ab binding at inflammation sites, prompting antibodies to relocate to environments with more favorable conditions. There, they can bind to self-antigens, initiating autoimmune processes. The enhanced binding in these environments, driven by microenvironmental changes such as low ionic strength, supports our theory that CO_2-induced autoimmunity arises from biochemical interactions mediated by pH and CO_2. Our work provides the first evidence linking CO_2 to epitope-paratope interactions in autoimmune contexts. Antibody structure may offer insights into the physicochemical properties of the target epitope. Boswell et al. found strong structural correlations between epitopes and their paratopes [52], while Stank et al. showed that single amino acid orientation within a binding pocket can modulate binding affinity [53]. Because epitopes often span just 4–6 amino acids, multiple macromolecules may share similar conformational and chemical characteristics. This can lead to cross-reactivity, where antibodies mistakenly bind to host antigens with similar epitopes [54], initiating autoimmunity.

Antibody kinetics and surface charge also influence tissue distribution, independent of antigen specificity. Electrostatic interactions between positively charged antibodies and negatively charged cell membranes can redirect antibody activity [52].

The thermic effect of CO_2 can increase antibody mobility, promoting escape from initial antigens and enhancing affinity for self-antigens. As CO_2 rises, generalized protonation strengthens electrostatic interactions, redirecting antibodies to self-targets. As hydrogen bond formation is exothermic, this reaction releases heat, further accelerating autoimmune interactions. These principles help explain how CO_2 catalyzes and sustains autoimmune reactions. In line with Almanza's findings, hypercapnic acidosis impairs lymphocyte self/non-self-discrimination, reinforcing our conclusions [55].

In summary, CO_2 catalyzes the initiation and maintenance of autoimmunity by providing optimal temperature and pH conditions, mediated by specific receptors, proteins, and signaling pathways.

Our results suggest that elevated CO_2 levels contribute to autoimmune damage in specific tissues such as cartilage and ligaments (e.g., in RA, SLE, diabetes), the gastrointestinal tract (e.g., in IBD, Celiac disease), and the skin (e.g., in vitiligo and urticaria). We propose that this tissue-specific damage is due to electrostatic interactions between the positively charged surface of antibodies and the anionic cell membranes of negatively charged tissues—interactions that are independent of antigen recognition. This hypothesis aligns with the findings of Veda et al. and Leal et al., who reported that the human body contains several negatively charged tissues, including the skin, joints, cartilage, ligaments, gastrointestinal mucosa, and vitreous humor of the eye [56,57] Furthermore, Nadal et al. provided evidence that gene expression patterns in response to heat stress are finely regulated at the mRNA synthesis level, leading to diverse phenotypic outcomes [33]. Mistrik et al. discussed the role of plasmonic nanoparticles (NPs), which, through light absorption and plasmon resonance, exhibit heat effects depending on their size, shape, and dielectric properties [32].

Carbon Dioxide Effects on Immune Cells and Signal Transduction. Several determinants influence the magnitude of autoimmune responses, including inflammatory cytokines, costimulatory signals, second messengers, and the cellular microenvironment. The interplay among CO_2, Ca^{2+}, and these determinants governs the overall immune outcome. Elevated CO_2 reduces pH, which increases extracellular adenosine concentrations [58]. These signaling cascades contribute to various physiological responses, including the sustained suppression of **NF-κB-dependent** immune regulatory cytokines that are essential for antibody class switching and immunological memory [30].

Antigen Presentation and T Cells. A critical component of immune defense is the interaction between activated antigen-presenting cells (APCs) and T cells. Antigen presentation by MHC molecules on APCs induces T cell receptor (TCR) internalization and gene rearrangement at the endogenous **TCRα** locus [59]. A key unanswered question remains: why do MHC–TCR immune complexes selectively bind to host antigens in autoimmune conditions, instead of microbial antigens? The answer may lie in CO_2-induced changes in ambient conditions, which alter the binding topologies of MHC–TCR complexes. Wucherpfennig et al. demonstrated that autoimmune complexes exhibit different binding orientations than anti-microbial complexes [60]. The thermo-acidotic effect of CO_2 contributes to membrane curvature and fluidity, facilitating topographic changes and mobilization of membrane-linked molecules, including MHC–TCR immune complexes.

Effect of CO_2 on Other Immune Cells. Inflammation negatively regulates memory precursor effector cell (MPEC) development. Notably, elevated CO_2 generates anti-inflammatory effects via acidification. It correlates with decreased migration of monocytes and macrophages and with reduced expression of inflammatory genes [61]. Proinflammatory cytokines such as IL-12 and IFN-γ are known to inhibit the development of immunological memory [62].

Antibody Diversity and B Cells. Autophagy plays a central role in B cell development and immune regulation. Our findings support a role for CO_2 in driving B cell-mediated autoimmunity, a conclusion reinforced by studies from Soboloff et al. and Raza et al. The Ca^{2+} channels STIM1 and Orai1, which act as sensors of temperature and acidosis, enhance autophagy under CO_2 influence. This process supports self-reactive B cells in evading autoimmune checkpoints and presenting autoantigens to T cells [17,63]. Autophagy also enables B cells to process and present peptides derived from self-antigens. Therefore, CO_2 may promote B cell autoimmunity via its thermo-acidotic impact on the **STIM1/Orai1–autophagy** signaling axis. Antibody diversity arises in part from errors during random recombination of gene segments. B cells can somatically mutate their immunoglobulin genes through recombination, hypermutation, and class-switching, primarily initiated by **activation-induced cytidine deaminase (AID)**, which deaminates cytosine [64].

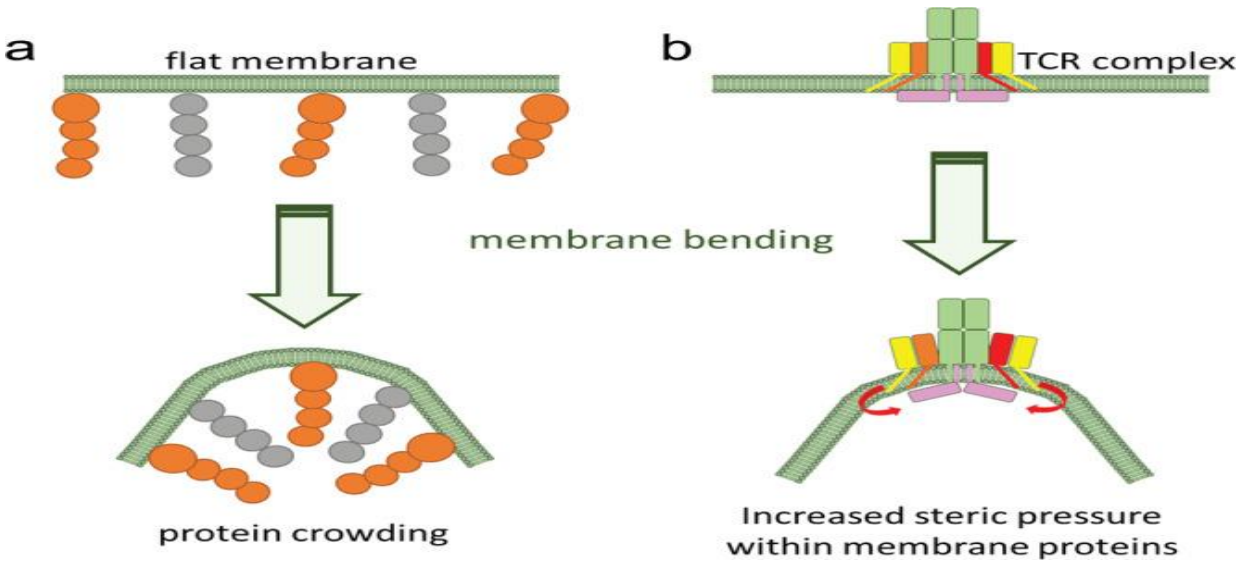
Our findings further affirm the biological relevance of heat-induced immune responses. Shiraz et al. demonstrated that somatically mutated high-affinity autoantibodies are a hallmark of autoimmune diseases [65]. Jaiswal et al. showed that somatic hypermutation introduces point mutations into immunoglobulin genes via cytosine deamination and error-prone uracil processing by base excision repair mechanisms [64]. Ehrlich et al. found that both DNA cytosine methylation and deamination are accelerated by heat [66], while Sethi attributed this acceleration to the protonation of phosphate groups in cytosine [67]. Mikocziova et al. revealed that certain B cell polarity proteins influence MHC gene expression by interacting with antigenic epitopes using identical Ig V genes [68].

Consequently, CO_2 may enhance B cell responsiveness to self-antigens by promoting somatic hypermutation and high-affinity autoantibody production through cytosine deamination, mediated by its thermal and protonation effects. Moreover, Blake et al. identified carbamate post-translational modifications—caused by CO_2 binding to N-terminal α-amino groups—as a part of CO_2's sensing and signaling functions [69]. Casalino et al. found that hypercapnia downregulates key immune genes, supporting the idea that CO_2 may contribute to antibody mutation and immune dysfunction [40]. In parallel, Zhao et al. showed that CO_2 suppresses catalytic antibody activity via carbamate inhibition—a mechanism that could help prevent autoimmunity [70].

Collectively, these findings support our conclusion that high CO_2 levels promote autoimmune disorders in a pH-dependent manner.

CO_2, T Cell Activation, and Function. The thermo-acidic properties of CO_2 uniquely influence T cell receptor (TCR) and B cell receptor (BCR) integrity and function. CO_2 modulates cholesterol accumulation and alters the topological architecture of membrane proteins, facilitating membrane bending and micro adhesion ring formation. Robinson et al. reported that plasma membrane cholesterol forms lipid rafts, which are critical for T cell signaling and activation. Therefore, targeting lipid metabolism may provide a promising therapeutic approach for autoimmunity [71,72]. TCR signaling is initiated by phosphorylation of **ITAMs** (immunoreceptor tyrosine-based activation motifs), which are essential for downstream signaling upon ligand binding [73]. Gaud et al. found that T cells expressing mutant TCRs with inactivated CD3ζ ITAMs (6F-CD3ζ) showed increased sensitivity to low-affinity ligands, enhanced cytokine secretion, and resistance to inhibitory signals. These cells also demonstrated heightened cytolytic activity against tumors expressing low-affinity antigens, suggesting novel approaches to TCR-based cancer immunotherapy [74].

Our findings provide novel evidence that thermally induced mechanical changes in membrane topology can affect surface receptor engagement. Al-Aghbar et al. reported that immune tolerance to heat-induced activation is mediated by curvature-driven release of CD3 from pMHC–TCR complexes [75]. Additionally, rapid Ca^{2+} influx may displace negatively charged phospholipids, releasing CD3 ITAMs from the plasma membrane and altering T cell responsiveness. It has been observed that the rapid influx of Ca^{2+} may compete with negatively charged phospholipids, thereby facilitating the release of CD3 ITAMs from the plasma membrane [76].



Protein Crowding and Membrane Bending

Figure 5 illustrates how proteins associated with biological membranes occupy larger surface areas on flat membranes (left) but become crowded in the inner leaflet when the membrane bends inward (right). This crowding generates steric pressure that resists membrane bending. Notably, bending the plasma membrane directly around engaged TCRs may increase steric pressure on the CD3 complex, facilitating the dissociation of buried CD3 ITAMs into the cytosol [75].

Summary of Mechanisms. CO_2 modulates MHC–TCR complexes at the T cell–APC interface through multiple mechanisms:

1. **Thermally induced mechanical membrane fluctuations** generate curvature around engaged pMHC–TCR complexes, releasing CD3 cytoplasmic domains.
2. **Protonation of negatively charged phospholipids** by CO_2 aids in the release of CD3 ITAMs from the plasma membrane. These changes may alter ligand affinity and reduce the ability to discriminate between self and non-self-antigens.
3. **CO_2-induced thermal stress** is associated with cellular stress signaling pathways, including heat shock proteins, which may enhance the translation of ribosomal DNA into proteins due to subcellular mobilization [77].
4. **Acidic microenvironments** directly shape T cell biology by modulating Ca^{2+} responses to TCR stimulation—responses necessary for full T cell functional competence and the prevention of autoimmunity. The resulting blunting of immune responses may contribute to tolerance.
5. Yang et al. [78] reported that **low pH inhibits IFN-γ**, leading to the **upregulation of Th17 cells**, which are involved in the pathogenesis of several autoimmune diseases.

In short. CO_2 plays a central role in orchestrating the immune response following disruptions in Ca^{2+} homeostasis.

Study Limitations. This study focuses on the roles of CO_2 and Ca^{2+}; therefore, future scientifically rigorous investigations should evaluate the additional impact of vitamin D. However, the key question remains unresolved: Is low vitamin D simply a reflection of disease severity, or does it represent an independent risk factor? Some studies present contradictory findings. For example, a meta-analysis reported that methylenetetrahydrofolate reductase (MTHFR) 677 C/T polymorphisms were associated with an increased risk of autoimmunity [79]. Nonetheless, the limited number of studies and heterogeneity among them may have weakened the strength of this evidence.

H. pylori and Extra-Gastric Autoimmunity. Our results revealed a surprising association between Helicobacter pylori infection and extra-gastric autoimmune chronic urticaria. We suggest that urease, by producing NH_3 and CO_2 from urea, contributes to CO_2 accumulation, which may underlie extra-gastric autoimmune manifestations, including urticaria. Supporting evidence from previous studies [80] indicates that H. pylori elicit numerous adaptive mechanisms, with urease identified as a key virulence factor necessary for colonization and survival.

Methodological Strengths. This study possesses several methodological strengths:

1. Participants were recruited from hospitals, with a relatively large sample size and robust case-control design. The data are representative of the target population, with minimal loss to follow-up and low recall bias.

2. Demographic matching of cases and controls was employed to minimize potential confounding.

3. Personal bias was unlikely to affect laboratory-based blood measurements.

CO_2 and Gastrointestinal Manifestations. The CO_2-induced gastrointestinal symptoms may be explained by prior studies from Abdelrazak, who found that H. pylori could be a causative agent of infant colic. He demonstrated that H. pylori LPS–activated TLR4 triggers IL-8 release from gastric epithelial cells, initiating inflammatory damage. The interaction between host immune factors and H. pylori virulence factors shapes the clinical outcome [80]. Furthermore, this inflammatory cascade induces Ca^{2+} influx, which amplifies IL-8–induced CO_2 signaling [81].

Revisiting Molecular Mimicry. Our findings challenge the conventional understanding of molecular mimicry. While some studies support this mechanism, others suggest that various infectious agents may protect against autoimmune diseases. This contradiction lends support to the **hygiene hypothesis**, which undermines the integrity of molecular mimicry theory [82].

We propose that **molecular mimicry is not the primary pathogenic mechanism** in autoimmunity. Instead, we argue that **inflammatory mediators and elevated autoreactivity** drive autoimmune disease. For instance, Komatsu et al. showed that Th1 $CD4^+$ cells, induced by IL-12, are essential for viral immunity [83]. Callahan et al. demonstrated that, during Campylobacter infection, dendritic cells and macrophages present C. jejuni antigens to T cells, which differentiate into Th1 and Th17 subsets, secreting IFN-γ and IL-17—cytokines involved in post-infectious autoimmune Guillain-Barré syndrome [84]. Similarly, Soderholm et al. reported that Th1 and Th17 responses are crucial for adaptive immunity against Group A Streptococcus pharyngitis, which leads to rheumatic fever and Sydenham chorea . [85]

Table 4. Conclusive Summary of Mechanisms Involved in CO_2-Mediated Autoimmune Development

Direct Effect	**Thermo-Acidotic Effect**	**Calcium Homeostasis Effect**
1. CO_2 exerts a "drill-like" action, forcing Ca^{2+} to enter cells. The increased intracellular Ca^{2+} influx amplifies the second messenger signaling generated immediately by CO_2 entry.	1. CO_2 inhibits antigen-antibody (Ag-Ab) interactions at sites of inflammation, forcing antibodies to migrate to nearby locations away from the local CO_2 effect. Once suitable conditions are met, these antibodies interact with self-antigens.	1. Dysregulated Ca^{2+} signaling is involved in the pathophysiology of autoimmune diseases.
2. CO_2-induced heating reversibly alters the electrical capacitance of plasma membranes, depolarizing target cells, triggering thermosensitive ion channels, and ultimately forming membrane pores that increase conductance and activate intracellular second messengers.	2. CO_2 protonation increases electrostatic interactions between anionic cell membranes and the positive charges of antibodies, orienting antibodies toward host antigens. This progression of autoimmunity is further magnified by antibody kinetics, which govern binding to other antigens in a manner independent of antigen recognition.	2. Specialized Ca^{2+} channels known as "STIMs" act as sensors of decreased Ca^{2+}, temperature increases, and acidosis.
3. Acting as a second messenger, CO_2 alters the expression of immune-related genes involved in immune tolerance.	3. The acidic milieu plays a critical role in regulating signaling cascades and Ca^{2+}-dependent transcription factors, which control gene activity.	3. Mutations in receptor proteins such as "Orai1" lead to decreased expression of several cytokines—including IL-1, IL-4, IL-17, IFNγ, and TNF-α—in $CD4^+$ and $CD8^+$ T lymphocytes, contributing to autoimmunity.
4. CO_2 acts as a central signaling hub in gene transcription and cytokine regulation.	4. The thermal effect of CO_2 induces curvature and fluidity in immune cell membranes, causing topographical changes and mobilization of membrane-linked molecules such as TCR-MHC complexes.	4. Altered Ca^{2+} signaling in lymphocytes leads to autoimmune and immunodeficiency syndromes.
5. CO_2 can activate signaling pathways and transcriptional alterations, leading autoreactive T cells to a state of activation.	5. CO_2 promotes B cell autoimmunity via its thermo-acidotic effects on the Ca^{2+} channel STIM1/Orai1 and autophagy pathways.	

Mediators involved: signaling pathways, Ca^{2+} channels, genes, second messengers, receptors, interleukins, and cytokines.

CONCLUSION

The implications of this study are far-reaching, opening new avenues for research into pathogenesis, treatment, and prevention of autoimmune disorders. With the rapid accumulation of immunological knowledge, it is anticipated that significant improvements will be achieved in the selectivity, efficacy, and pharmacokinetics of immune-modulating drugs. **CO_2 penetrates cell membranes and acts like an "electric drill,"** forcing Ca^{2+} to enter the cell against its concentration gradient—a mechanism referred to as the "CO_2 drill-like action." CO_2-induced heating reversibly alters the electrical capacitance of the plasma membrane, depolarizing the target cell, affecting ion channel gating, and forming transient membrane pores. **The autoimmune-inducing mechanism of CO_2, driven by both thermal and protonation effects,** uniquely influences the structure and function of both T-cell receptors (TCRs) and B-cell receptors (BCRs). These effects are mediated through cellular cholesterol modulation and topological changes in membrane architecture, leading to membrane bending and the formation of micro-adhesion rings. **Somatically mutated high-affinity autoantibodies** may be generated through CO_2-induced thermal cytosine deamination and protonation, which dissociates phosphate groups that attack cytosine amino groups. Furthermore, CO_2-induced mutagenesis may be amplified by autoimmune susceptibility genes encoded in the major histocompatibility complex (MHC).

Research Implications.

1. Continued investigation into the role of CO_2 in autoimmune disease pathogenesis should become a primary focus of future studies. This includes the identification of genes involved in CO_2-mediated immune responses, prediction of mutations affecting immune signaling, and elucidation of their downstream effects on immune cell function.

2. Understanding the pivotal role of CO_2 in modulating immune responses is essential to improving the design of therapeutic monoclonal antibodies. The evidence presented here linking CO_2 to autoantibody generation may inspire future clinical trials aimed at addressing the persistent problem of antibodies targeting urease. Developing next-generation urease inhibitors with minimal side effects could not only eradicate Helicobacter pylori and its complications but also prevent autoimmune progression by reducing sustained CO_2 buildup, which is essential for H. pylori survival.

3. Novel therapeutic approaches should be explored to counteract intracellular CO_2 accumulation. This includes strategies to deplete rising CO_2 levels or block its intracellular diffusion. One potential method is the application of hyperbaric oxygen therapy to neutralize the harmful effects of CO_2. These modalities offer promising potential for broad application in the pharmaceutical industry, including the development of immunologic modulators for both autoimmune diseases and cancer.

4. Targeting Ca^{2+} channels involved in autoimmune responses requires precise strategies to ensure drug specificity and minimize off-target effects. It is critical to understand how therapeutic agents interact with distinct Ca^{2+} channels to reduce cross-reactivity and tissue damage, and to enhance therapeutic efficiency.

5. Our study raises several compelling questions that warrant further investigation into cellular ion channels, signaling pathways, and altered receptor protein structures. These elements represent promising targets for mitigating their downstream pathological effects in autoimmune conditions.

Abbreviations.

Molecular Mimicry = similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by a foreign-derived antigen in a susceptible individual.

PIP = Phosphatidylinositol 4-phosphate.

ER/SR = Endoplasmic reticulum/ Sarcoplasmic reticulum.

Transient receptor potential channels = TRPCs

cAMP = Cyclic adenosine monophosphate.

NFκB = Nuclear factor kappa of B cell.

RA= rheumatoid arthritis.

SLE= Systemic lupus erythematosus.

IBD= Inflammatory bowel diseases

Ig V = Immunoglobulin variable chain.

Ag-Ab = Antigen Antibody.

RGS = Regulator of G-protein signaling.

APCs = Antigen presenting cells.

MHC = Major histocompatibility complex.

TCRs = T cell receptors.

ITAMs = Immune-receptor Tyrosine-based-Activation-Motifs

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