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ORIGINAL RESEARCH ARTICLE

Expression of HIF-1α in pediatric asthmatic patients

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ABSTRACT

Background: Several studies have suggested that HIF-1α regulates eosinophil activity and induces epithelial inflammation *via* NF-ϰB activation in the pathophysiology of asthma. The purpose of this study was to examine the expression of the transcription factors HIF-1α and nuclear HIF in mononuclear cells obtained from peripheral blood samples of healthy pediatric patients, asthmatic patients, and asthmatic exacerbations, regardless of disease severity.

Methods: HIF-1 levels were measured using immunocytochemistry in 133 patients aged 6 to 17 years in this cross-sectional and comparative study. A microscope was used to examine glass slides, and positive cells were counted in four fields per slide using an image analyzer.

Results: HIF-1α and nuclear HIF levels were significantly higher in asthma patients and even higher in patients experiencing asthma attacks ($p<0.0001$, 95% CI). There was no significant difference in the percentage of HIF-1α expression between groups with intermittent asthma and those with mild persistent asthma, nor between patients with asthma and those experiencing asthma exacerbations.

Conclusions: When compared to healthy individuals, the expression of nuclear HIF and HIF-1α is increased in peripheral mononuclear cells in asthma patients and even more so in asthma exacerbations. This suggests that HIF-1α is important in the pathogenesis of this disease.

Key words: asthma; HIF-1α; asthmatic exacerbation; airway remodelling; pediatric.

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Introduction

Asthma is a chronic inflammatory disease that affects more than 300 million people around the world. It causes a variety of symptoms such as shortness of breath, wheezing, coughing, and chest tightness. These symptoms are caused by a combination of factors such as airway remodeling, bronchoconstriction, mucus secretion, and airway hyperresponsiveness [1-3].

Airway remodeling is responsible for the persistent airflow obstruction seen in asthma patients. This phenomenon is characterized by morphological changes in bronchiole cells and tissues. Extracellular matrix protein deposition, smooth muscle thickening, goblet cell hyperplasia, increased vascularity, epithelial damage, and ciliary dysfunction are all symptoms. The persistent airway inflammation associated with asthma is driven by eosinophils, which are activated by IL-5, released by Th2 cells and type 2 innate lymphoid cells (ILC-2). This activation leads to the expression of Th2 cytokines (IL-4, IL-5, IL-9, IL-13, and IL-25) as well as acute proinflammatory cytokines [1,4,5].

Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription factor composed of two subunits, HIF-1α and HIF-1β [6]. HIF-1α, with a half-life of 5-8 min, serves as a central regulator of cellular oxygen levels. It achieves this by activating genes responsible for modulating oxygen homeostasis and plays a pivotal role in inflammatory and immune responses [7,8]. HIF-1α is continually synthesized in cells during hypoxic conditions, where it accumulates and translocates to the nucleus to promote the expression of hypoxia-responsive genes. These genes include GLUT-1, erythropoietin (EPO), and vascular endothelial growth factor (VEGF), which, in turn, facilitate angiogenesis, vasodilatation, vascular permeability, and glucose uptake [9,10]. In hypoxic conditions, HIF-1α also inhibits mTOR signaling, a critical pathway for protein synthesis and cell growth. However, HIF-1α can also become activated under normoxic conditions during inflammatory responses triggered by transforming growth factor beta (TGF-β), lipopolysaccharides (LPS), tumour necrosis factor-alpha (TNF- α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [6,11].

Several studies have suggested a pivotal role for HIF-1α in the pathophysiology of asthma, as the inflammatory process and bronchoconstriction contribute to hypoxia [5,12]. HIF-1α not only regulates eosinophil activity, but also promotes epithelial inflammation through NF-κB activation. Furthermore, it induces vascular permeability and triggers an inflammatory response by transcriptionally activating inducible nitric oxide synthase (iNOS) and VEGF [12]. VEGF, being the primary regulator of angiogenesis, serves as a significant mediator in airway inflammatory diseases and is among the target genes of HIF-1α. It has been proposed that HIF's role is, in part, mediated by the up-regulation of VEGF in the allergic airway response [13].

VEGF is synthesized by lymphocytes, eosinophils, macrophages, and neutrophils, and it holds a crucial role in Th2-mediated inflammation [9,10]. The impact of this glycoprotein on airway remodeling is well-established, with VEGF concentrations in sputum and lung tissue demonstrating a positive correlation with the severity of bronchial asthma. Moreover, up-regulation of VEGF leads to elevated levels of IL-4, IL-5, and IL-13 [5,10,14].

mTOR, a serine/threonine kinase belonging to the phosphoinositide 3-kinase (PI3K)-like kinases, serves as the principal regulator of metabolism and cell growth. In the context of asthma pathophysiology, it has been observed that PIK3/Akt modulates airway hyperresponsiveness and vascular permeability by regulating VEGF expression, which is mediated by HIF-1α activity [15]. Additionally, other studies have highlighted the role of PI3K in the Th2 response, as its inhibition resulted in reduced hyperresponsiveness, airway inflammation, and vascular permeability in a murine model of asthma [16].

The role of HIF-1α in other immune cells, such as dendritic cells (DCs) and monocytes, has been investigated. The oxygen gradient is a crucial factor influencing the migration of monocytes and DCs to inflammatory sites. This gradient upregulates the expression of adhesion molecules and chemoattractants like VEGF, endothelin, and CXCL12. When monocytes and DCs are exposed to hypoxic environments, HIF-1α levels increase, leading to the augmentation of HIF-1α target genes involved in glycolysis. This adaptation is necessary to compensate for the hypoxic environment by providing alternative energy sources. Additionally, glycolysis promotes DC maturation and T-cell activation by DCs [17,18].

Therefore, taking into account the significance of HIF-1α in the pathophysiology of asthma, the main goal of this study was to assess the expression of the transcription factor HIF-1α in mononuclear cells obtained from peripheral blood samples of healthy pediatric patients, those with asthma, and those experiencing asthma attacks, regardless of severity. These measurements were then compared among the subgroups under investigation.

Materials and Methods

A descriptive, cross-sectional, and comparative study was conducted involving 133 participants aged 6 to 17 years. This group comprised 53 scholars and teenagers previously diagnosed with asthma, 27 patients who had experienced an asthma exacerbation, and 53 healthy individuals. The study was carried out at two Pediatric Hospitals in México City, México. Inclusion criteria encompassed individuals diagnosed with asthma for a minimum of one year who also demonstrated a positive reversibility test during that same year. Exclusion criteria included individuals with asthma who had been treated with beta-two (β_2) agonists more than twice a week, received inhaled or systemic steroids within the three months prior, had any infectious respiratory disease, or reported passive or active tobacco use. After obtaining consent from their legal guardians and patient assent, participants underwent a comprehensive medical history assessment focused on their current symptoms. Additionally, a blood sample was collected for processing in the laboratory. In the case of patients experiencing an asthma exacerbation, they had been previously diagnosed with asthma before their hospitalization, and their classification was based on clinical parameters and the guidelines outlined in the Global Initiative for Asthma (GINA) report.

The purification of peripheral blood cells was performed as follows: mononuclear cells were isolated using gradient centrifugation with Ficoll-PaqueTM PLUS from GE Healthcare, Sweden. Upon successful isolation, 10,000 cells/μL were placed on a glass slide, and PBS 1× was added to ensure optimal preparation. This value was then multiplied by the number of slides used (25×75 mm Madesa México).

To minimize experimental variation, the HIF-1α protein reaction was synchronized for all groups. Sodium citrate was employed for antigen retrieval, followed by a 20-min boiling step in a water bath. To eliminate endogenous peroxide activity, methanol and 3% hydrogen peroxide were used three times for 10 min each. Nonspecific antibody binding was blocked using 2% normal pig serum in PBS 1×. Subsequently, the tissue sections were left to incubate overnight at room temperature with the polyclonal anti-HIF-1α antibody.

Furthermore, the tissue sections were incubated with a second antibody conjugated to biotin, followed by streptavidin conjugated to HRP (horseradish peroxidase). The color reaction was achieved by adding diaminobenzidine substrate (DAB) for 2 min. The reaction was halted with water, and the cells were counterstained with hematoxylin. Once cell dehydration was evident, they were mounted with resin. Glass slides were examined using a microscope (Olympus, BX-40), and positive cells, identifiable by their brown color, were quantified in four fields per slide using an image analyzer (Image-Pro Plus, Media Cybernetics, Silver Spring, MD, USA).

The database was established using IBM® SPSS Statistics software. Descriptive statistical data were generated, including mean, standard deviation, standard error, frequency, and confidence intervals. To comprehensively analyze the data, we employed the analysis of variance (ANOVA) *post-hoc* test to compare the three groups and an independent samples *t*-test to compare the healthy and symptomatic groups, with a significance level of 0.001.

Results

Out of the 133 patients, 73 were men, and 60 were women. Among them, 53 had been diagnosed with asthma, 27 were experiencing asthma exacerbation and had sought treatment at the hospitals, and 53 were healthy subjects (Figure 1). In the group of individuals with asthma, the average age was 12.2 years. In the asthma exacerbation group, the mean age was 9.5 years, and in the healthy control group, the average age was 12 years old. Within the asthmatic group, as per the GINA criteria, individuals were categorized based on the severity of their condition. Specifically, 34 patients had controlled asthma, while 19 exhibited partially controlled asthma. Moreover, among those with acute asthma, 20 patients experienced mild exacerbation, five had moderate exacerbation, and two faced severe exacerbation (Table 1). Significant differences were observed in the expression of both HIF-1α and nuclear HIF among the three groups: patients with asthma, patients experiencing asthma exacerbation, and healthy controls ($p<0.0001$, 95% confidence interval, standard deviation). The control group exhibited an average HIF-1α expression of 21.4%, while individuals with asthma had a mean expression of 63.53%. In the asthma exacerbation group, the mean expression was notably higher at 96.91% (Table 2). Concerning the expression of nuclear HIF, the mean expression in the healthy control group was 2.83% ($p<0.05$, 95% confidence interval 1.60-4.06). In the group of individuals with asthma, the mean expression was 5.85% ($p<0.05$, 95% confidence interval 3.92-7.78), and in the group of patients experiencing asthma exacerbation, the mean expression of nuclear HIF was notably higher at 33.65% ($p<0.05$, 95% confidence interval 25.56-41.73). No statistically significant difference was observed in the percentage of HIF-1α transcription factor expression between the controlled asthma group and the partly controlled asthma group. Similarly, no significant disparity was found in the expression of this transcription factor between the asthmatic and asthma exacerbation groups.

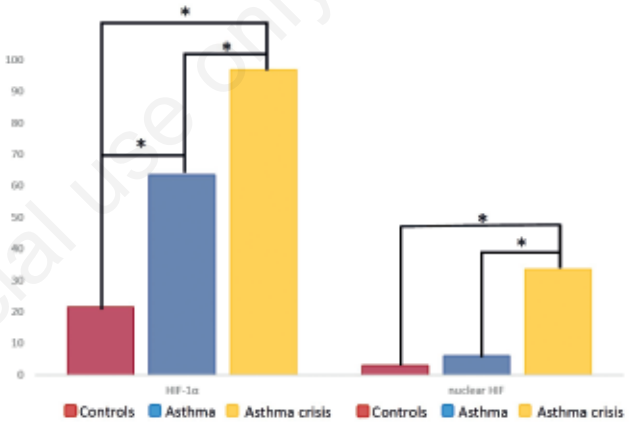

Figure 1. Comparison of values and confidence intervals (CI 95%) between the groups. *p<0.0001.

Table 1. Demographic characteristics of each group.

	Subjects	Age	Age SE	Gender	
				Male	Female
MIA	34	12	0.25	21	13
MPA	19	12.56	0.64	10	9
Asthma exacerbation	27	9.52	0.58	15	12
Control	53	12.02	0.22	27	26
Total	133	12.1	0.17	73	60

MIA, intermittent asthma; MPA, mild persistent asthma; SE, standard error.

Table 2. Results of the expression of HIF-1α and nuclear HIF.

	Subjects	Gender		Standard deviation	HIF-1α (%)		HIF-n (%)	
		Female	Male		CI 95%	Mean	CI 95%	Mean
C	53	26	27	1.59	16.83-25.97	21.4	1.60-4.06	2.83
Asthma	53	22	31	2.02	57.49-69.56	63.53	3.92-7.78	5.85
AE	27	12	15	2.95	94.67-99.15	96.1	25.56-41.73	33.65

C, control group; AE, asthma exacerbation group.

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Discussion

Asthma is a chronic inflammatory disease that leads to airway remodelling, characterized by morphological changes. These changes are controlled by the overexpression of transcription factors, which in turn overregulate growth factors and cytokines [1,3]. During the tissue remodeling process, angiogenesis plays a significant role, resulting in an abnormal increase in both the number and size of bronchial microvasculature. In this context, there is an overexpression of VEGF and HIF-1α [5,7,19].

The initial studies of HIF-1α expression focused on *in vivo* experimental models, which demonstrated an increase in HIF-1α expression in mice with induced allergic inflammation when compared to healthy mice [20]. Another study, based on murine pulmonary allergic inflammation, concluded that HIF-1α expression is correlated with the expression of cytokines involved in tissue remodeling associated with asthma [21]. Crotty *et al*. [22] conducted a study to explore the role of HIF-1α in myeloid cells in the pathogenesis of asthma. They utilized HIF-1α knockout mice in myeloid cells. Interestingly, these mice did not develop airway hyperresponsiveness. However, it did not prevent the activation of other allergic inflammatory mechanisms. This suggests that HIF-1α may be activated in other cell types, such as epithelial cells, smooth muscle cells, endothelial cells, and others. These, in conjunction with other inflammatory mechanisms, contribute to the pathogenesis of asthma. Hypoxia-related responses have been extensively documented in various studies, and the role of HIF-1α in response to hypoxia is well-established. However, it was the scarcity of studies examining this factor in asthma patients that motivated this investigation. In this study, we assessed the expression of HIF-1α, nuclear HIF, and the transcription factor for HIF-1α in both healthy pediatric patients and those with asthma, including those experiencing an asthma exacerbation.

It is worth noting that this methodology had not been previously employed to determine the expression of this factor. Previously, its expression had been indirectly identified through the estimation of bronchial tissue obtained via bronchoscopy [13,23-25]. Even though we adapted the methodology for our pediatric sample to make it a less invasive procedure, our results remained consistent with those found in existing literature, indicating an increased expression of HIF-1α in asthmatic patients when compared to healthy individuals.

While the role of HIF-1α as a biomarker for asthma has not been extensively documented, it has been implicated in other conditions, such as idiopathic pulmonary fibrosis (IPF). The role of HIF-1α in IPF, as described in the study by Zhou *et al*. [26], parallels what we have found in our research. It not only contributes to the pathogenesis of IPF but also shows potential as a predictor of disease progression and an independent predictor of mortality. Zhou *et al*. utilized a validated HIF score based on a 15-gene expression signature within the HIF pathway.

Additionally, HIF has been associated with the pathophysiology of chronic obstructive pulmonary disease (COPD), a condition that shares similarities with asthma in terms of its pathophysiology. Given their involvement in these crucial physiological processes, HIFs could potentially serve as biomarkers for certain lung conditions. However, further research would be required to confirm this hypothesis [27].

Another noteworthy aspect of our study was the comparison between subgroups of asthmatic patients. Patients experiencing asthmatic exacerbation exhibited an increased expression of the studied factor when compared to non-exacerbation asthmatic patients. The elevation in proinflammatory cytokines and the expression of genes associated with airway remodeling in asthma patients following allergen exposure has been demonstrated in bronchial tissue biopsies [3,28,29]. The heightened expression of HIF-1α observed in asthmatic exacerbation aligns with the clinical presentation of these patients. Their greater disease severity and higher frequency of exacerbations result in air flow limitations, decreased pulmonary function, and bronchial hyperreactivity, ultimately leading to airway remodeling [3,30]. The expression of HIF-1α nuclear indicates transcriptional activity, and in our study, this expression was notably higher in the group of patients experiencing asthmatic exacerbation compared to both asthmatic patients and healthy individuals. Patients treated with ICS/OCS were excluded from the analysis, as these drugs are known to downregulate HIF-1α levels and HIF transcriptional activity [31]. These findings suggest that HIF-1α activity is heightened in asthma and further amplified during acute episodes [30,32].

However, it's important to acknowledge the limitations of our study. The sample size was relatively small, consisting of patients treated at two hospitals. Additionally, not all factors contributing to airway remodelling were considered. We opted for a non-invasive procedure due to the pediatric population under study, but we recommend that future research combines both methodologies to provide both direct and indirect measurements of HIF-1α. Moreover, future investigations should explore HIF-1α in conjunction with other mechanisms that induce airway remodeling to discern differences among asthma subgroups based on disease severity.

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