Al-Kunooze Scientific Journal
e-ISSN: 2706-6223
P-ISSN: 2706-6231
https://www.asj.kunoozu.edu.iq/
2026, 12(3):31-45

Hypoxia promotes cellular apoptosis in blood cells through P53 activation in patients with Diabetes

Azhar A . Ameen[1], Zeyad abdulkadhim mazyed [2], Suhyila Fadhil Ali[3]

[1,2,3] Department of Biology, College of Science, University of Basrah, Basrah, Iraq,
Correspondence author: azhar.ameen@uobasrah.edu.iq

- Receive Date **14 March 2026** Revise Date **17 April 2026**
- Accept Date **17 April 2026** First Publish Date **25 June 2026**

https://doi.org/10.36582/ksj.2026.170052.1034

Abstract

Hyperglycemia in diabetes promotes Hypoxia leading to alterations in the cellular microenvironment, Hypoxia triggers adaptive cellular responses, that are largely regulated via a transcription factor called Hypoxia inducible factor 1 -alpha (HIF-1α),in addition Hypoxia influences cell death pathways through the stabilization of the tumor suppressor factor p53.Aims: this study aims to assess the impact of hypoxia inducible factor (*HIF-1α*) in regulating *p53* signaling in those with type 2 diabetes in comparison with the control group. Whole blood samples were obtained from both diabetes and non-diabetic participants, followed by quantitative PCR (qPCR) to estimate the relative transcriptional levels of (*HIF-1α* and *p53*). The results showed a significant up regulation in the expression of *HIF-1α* and *p53*inpatientsrelative to the control group, Analysis of covariance (ANCOVA) revealed that the overall model for *HIF-1α* and P53 expression was statistically significant, while diabetes status, gender and body mass index (BMI) did not show significant in dependent effects. Additionally a notable positive correlation was observed between expression of *HIF-1α* and *p53*. The study illustrated that a potential impact of the*HIF-1α* signaling in inducing cellular apoptosis through the upregulating of *p53*, these results provide evidencethat*HIF-1α* and *p53* may act as interconnected cellular markers and support further investigation in expanded cohorts.

Keywords: Cellular apoptosis**,** Hyperglycemia, Blood microenvironment, Diabetes mellitus, Hypoxia inducible factor.

Published by: Al-Kunooze University, Basrah, Iraq

Introduction

Cellular survival in eukaryotic cells depend on oxygen consumption for various cellular functions , therefor stable homeostasis of oxygen is a critical for the maintenance the modulation of regular cellular processes, and any deviations in oxygen levels induce stress and may modulate the homeostasis regulating proteins and genes , deprivation of oxygen or hypoxia and the induction of hypoxia-inducible factors , contributing to cellular injury and the progression of multiple pathological processes [1]. Oxygen homeostasis is fundamental for cell viability and function in all metazoan cells , Hypoxic conditions arise when oxygen utilization surpasses oxygen supply, triggering the activation of Complex adaptive mechanisms that enable cell survival through hypoxia , these response involve metabolic remodeling of mitochondrial respiration via oxidative phosphorylation to glycolysis under anaerobic environment, enhanced erythropoiesis , differentiation, angiogenesis, proliferation and migration , defective cellular adaptation due to the hypoxia associated with the pathophysiology of various diseases [2] .

Hypoxia conditions trigger the promotion of the heterodimeric critical transcription factor *HIF-1. Under low oxygen conditions, HIF-1α undergoes stabilization and produces a dimer with the HIF- β subunit. This complex regulates* multiple cellular processes, including cell proliferation, metabolic alteration, and angiogenesis, all of which may contribute to tumor development [3] .

Hypoxia has an effective role in the induction of autophagy, and disruption of normal physiological autophagy could promote apoptotic pathways. [4]; [5].

The tumor suppressor protein *p53* , a transcription factor that responds to stress, manages cell survival and death to prevent tumor growth. P53 also influences metabolic pathways and responds to alterations in metabolism, as demonstrated in both in vitro and animal studies. [6]

p53 is a homo-tetrameric protein encoded within the p53 gene , and serves as a potent transcription factor that encodes DNA-binding proteins. It modulates multiple biological processes, for instance: the cell cycle, apoptosis, cellular senescence, cellular differentiation, energy metabolism, and DNA repair[7] [8].

[9] hypothesized that elevated glucose interferes with *HIF-α* signaling via a mechanism associated with *p53* activity, leading to the remodeling of cellular metabolism through changes in the rate of oxygen uptake and enhanced glycolytic pathway.

*p53*activation has been related toβ- cell apoptosis in vitro, and has also been observed in diverse diabetic mouse models under diabetic conditions [10].

Evidence suggests that hyperglycemia and diabetes disrupt *HIF-α* signaling pathway and cell metabolism through a p53 upregulation-mediated mechanism. In vitro, *p53* stimulation in cardiomyocytes counteracted hyperglycemia-induced a decrease of *HIF-α* signaling, and promoted metabolic reprogramming by decreasing oxygen consumption [9]. Moreover, the

interaction between *HIF-1α* was confirmed by Co-immunoprecipitation, demonstrating that *HIF-1α* influenced cellular cycle control and proliferation via *p53*-mediated signaling [11] .

The current investigation assessed the levels of*HIF-1α*under hypoxic conditions in diabetes to determine its involvement in promoting cell damage by activating *p53*.

Methods

Participants

A total of 40 consenting subjects participated in the current study. The participants were assigned into patients and control groups, with 20 members in each group. All subjects completed a detailed questionnaire, and permission was obtained for whole blood sampling and measurement of *HIF-1α* and *p53* . Ethical approval for the study was obtained from the university of Basrah . Approximately (3-5 ml) ofperipheral blood were sampled into (EDTA) containing tubes and cooled on ice, and kept it at -80 °C until further analysis .

Quantitative real- time PCR

Total RNA was purified from whole blood through the Geneaid kit according to the manufacturer's guidelines. The purity and quantity of the extracted RNA were measured at 260 / 280 nm via Nano-Drop spectrophotometer (Mecasys Co, Korea). Subsequently , complementary DNA (cDNA) was synthesized from the extracted total RNA using the UniScript (Genes and Bitotech) (Cat. No. SR512).

Quantitative real-time PCR (RT-qPCR) for *HIF-1α* and other genes was performed by the(SYBR Green PCR Master Mix total RNA) , following the union script protocol (Gene Script and Bitotech , Cat. No. SR512) . The primers for *HIF-1α* and other gene were synthesized by TaKaRa company, The study employed the following primer sequences : *HIF-1α* : forward 5'-ACTAGCCGAGGAAGAACTATGAA-3' , and reverse :5'-TACCCACACTGAGGTTGGTTA-3, *p53* : 5′-TAACAGTTCCTGCATGGGCGGC3', and reverse : 5'-AGGACAGGCACAAACATGCACC-3′-3 , with Beta actinchosen as the reference gene Forward:5′-GGCACCCAGCACAATGAAG-3′Reverse: 5′-CCGATCCACACGGAGTACTTG-3′.
Gene expression level of each gene was quantified using the 2^−ΔΔCt method, and results were presented as fold change relative to the control group . All RT-qPCR reactions were carried out in triplicate.

Statistical analysis

Statistical analysis was assessed using IBM SPSS Statistics(25.0), Statistical significance was considered as $P < 0.05$, data distribution's normality was assessed using the Shapiro Wilk , and Kolmogorov-Smirnov tests , comparison between groups were detected by used independent T-Test for parametric data which expressed as the

mean ± SD , and Mann Whitney U test for non-parametric data which expressed as the median and interquartile range (IQR): (Q1-Q3), , In order to avoid potential bias, analysis of covariance (ANCOVA) was performed to adjust for covariates of baseline

values (dependent variable) such as BMI and gender. Finally, correlations between the expression levels of the *HIF-1α* and *P53* were investigated using Spearman's correlation coefficient.

Results

This study was conducted a total of 40 participants. The control group was constituted of20 healthy individuals 10 males (50%) male and 10 female (50%) , and the patients group included 20 subjects 10males (50%)and 10 females (50%) . The mean ± SD of age for the patients group was (52 ± 10.32) and (49± 7.81) for the control group. Body mass index (BMI) was calculated and recorded for all participants. The mean of BMI was (30.54±4.91) kg\m2 for the patients group and (25.07 ± 4.04) kg\m2 for the control group. The mean of Fasting blood glucose for the patients group was (145±31.56) mg/dLand for the control was (84± 6.82) mg/dL. The mean of HbA1c levels in the patients group were (7.66 % ± 1.94) and (4.80% ± 0.95) for the control group.(Table 1).

Table1. **Comparison of clinical factors between the control group and the patient group**

Variables	Control group	Patients group
Age	49 ± 7.81	52 ± 10.32
FBG mg/dL	84 ± 6.82	145 ± 31.56
BMI kg\m^2	25.07 ± 4.04	30.54±4.91
HbA1c %	4.80 ± 0.95	7.66 ± 1.94

Expression of *HIF-1α*

Figure 1.Illustratedthat the expression of *HIF-1α* was up regulated in the patient group(2.93 fold) relative to the control group .The mean expression level were (2.4679± 0.7315) and(0.9182 ± 0.4760) for patients and controls group, respectively ; (P< 0.01), with statically difference between group (P< 0.01).

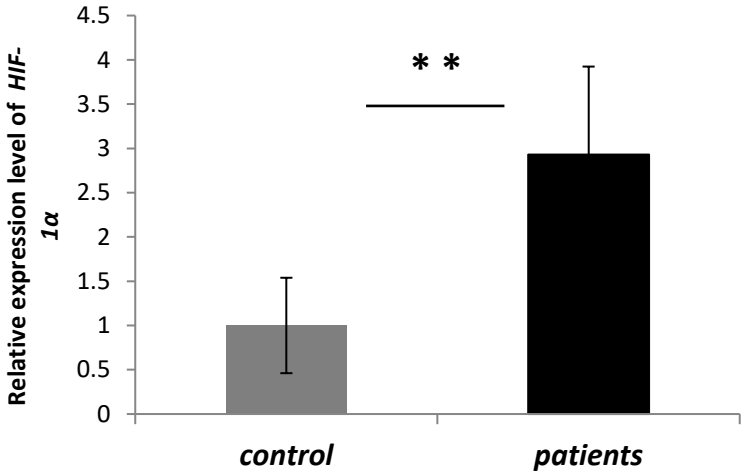

Figure1. **Comparison of the relative expression of *HIF-1α* between the control and patient group. Data are presented as a fold change. An independent t-test was used to assess the statistical differences between groups, (**P< 0.01).**

An ANCOVA was conduct to examine the effects of diabetes status, gender ,and BMIon *HIF-1α* gene expression after adjusting for covariate .The analysis (table2) showed that the overall model was statistically significant, F (6,33) = 10.11, p < 0.001, explaining64.8% of the variance (R^2 =0.648). However ,no significant main effects were observed for diabetes (F(1.33) =0.03 , P=857), gender (F(1.33) =0.18, P=0.675), or BMI (F(1.33) =O.43 , P=0.515) on *HIF-1α* gene expression. The adjusted estimated marginal means and the interaction trend between diabetes and gender are demonstrated in (figure 2).

Table 2 . Analysis of covariance (ANCOVA) for the effects of diabetes , gender, and BMI on *HIF-1α* gene expression.

Source	df	F	P-value	Partial η^2
Diabets	1	0.03	0.875	0.001
Gender	1	0.18	0.675	0.005
BMI	1	0.43	0.515	0.013
Diabets * Gender	1	0.10	0.752	0.003
Gender * BMI	1	0.18	0.676	0.005
Diabets * BMI	1	1.70	0.201	0.049

*Partial Eta Squared represents effect size

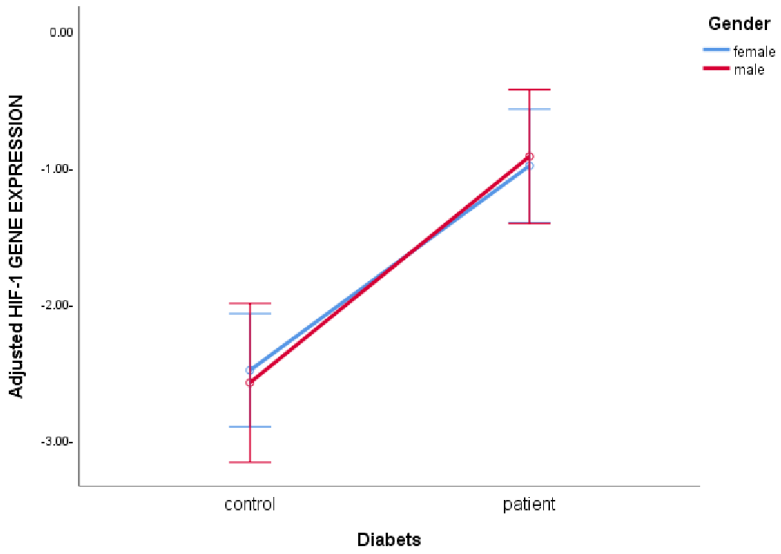

Figure 2 .Interaction plots of the estimated marginal means of adjusted *HIF-1α* gene expression by diabetes and gender status. Values represent adjusted mean ± 95% confidence intervals (derived from ANCOVA).

Expression of *p53*

Figure (3) showed a significant up regulation in *p53* in patient group (3.256 fold) relative to the control group . Δct values showed that the median expression level were 1.1400 (IQR: 0.833 - 1.373)and 2.936 (IQR: 2.686 - 3.103) for patients and control group were respectively: with statically difference between group (P< 0.01).

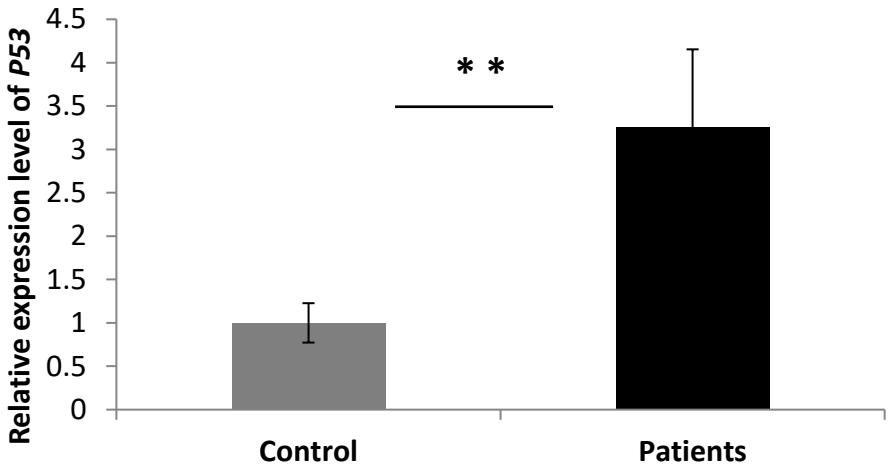

Figure 3 .Comparison of the relative expression of *p53* between the control and patient groups. Data are shown as fold change. Statistical differences between group was assessed by the Mann Whitney U test to assess differences between groups (P< 0.01).**

An ANCOVA was conducted to examine the effects of diabetes status, gender , and BMI on *p53* gene expression after adjusting for covariates. And the analysis (Table 3) showed that the overall model was statistically significant , F (6, 33) = 44.11, p<0.001, explaining 88.9% of the variance (R^2 =0.889) . However, no significant main effects were observed for diabetes (F:1.33) = 0.31, P = 579), gender (F(1.33) =2.96 , P = 0.095) ,or BMI (F:1.33) = O.97, P = 0.323) on *p53* gene expression . The adjusted estimated marginal means and the trend of interaction between diabetes and gender are demonstrated in Figure 4)

Table 3 . Analysis of covariance (ANCOVA) for the effects of diabetes , gender, and BMI on *p53* gene expression.

Source	df	F	P-value	Partial η^2
Diabets	1	0.31	0.58	0.009
Gender	1	2.96	0.095	0.082
BMI	1	0.97	0.33	0.029
Diabets * Gender	1	4.14	0.05	0.112
Gender * BMI	1	1.89	0.178	0.054
Diabets * BMI	1	3.06	0.09	0.085

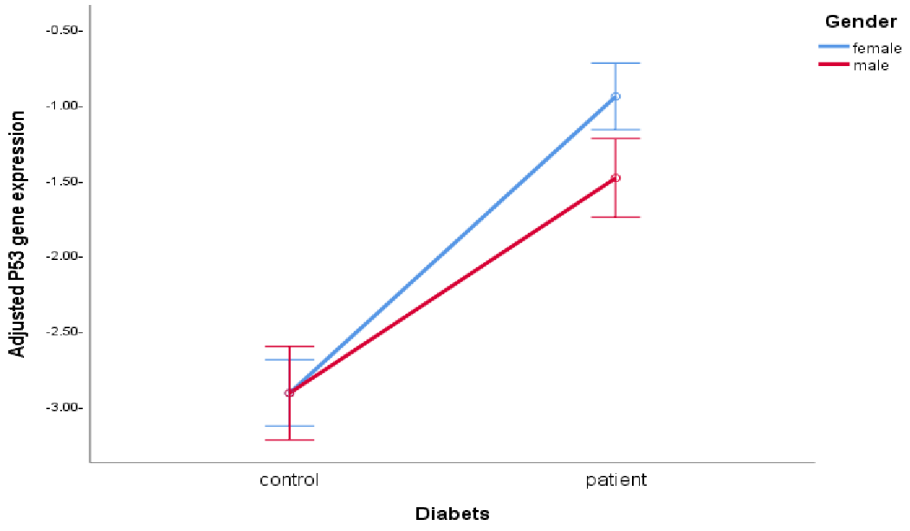

Figure 4. Interaction plots of the estimated marginal means of adjusted *p53* gene expression with diabetes and gender status, values represent adjusted mean ± 95% confidence intervals derived from ANCOVA.

Correlation analysis between the expression levels of *HIF-1α* and *p53*

A statistically significant positive correlation was observed between the relative expression levels of *HIF-1α* and *p53* , with a Spearman's correlation coefficient (R) of 0.68 ($p < 0.01$), as shown in Figure 5.

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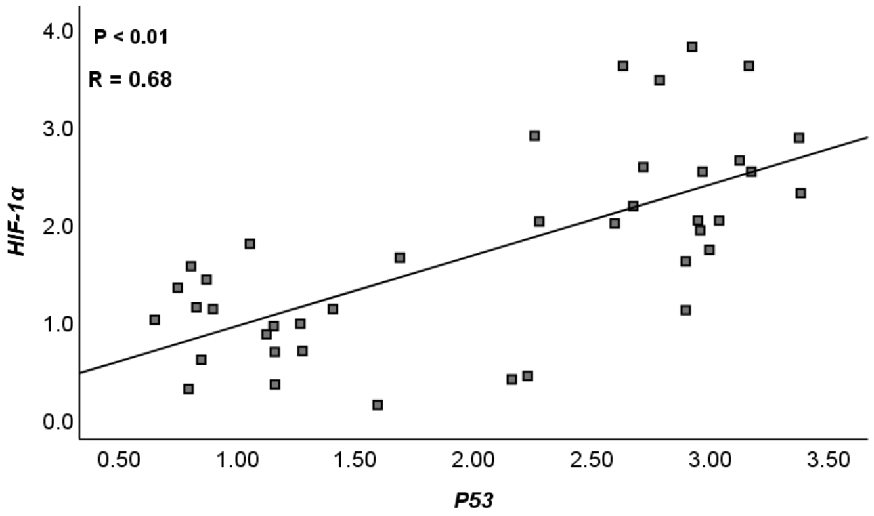

Figure 5. Spearman's correlation analysis between the expression levels of *HIF-1α* and *p53.*

Discussion

The current study investigated the correlation between hyperglycemia and hypoxia condition and their combined effects on the levels of *HIF-1α* and *p53*. Diabetes is characterized by hypoxia in multiple tissues, but appropriate hypoxic adaptation is impaired as a result of reduced activation of *HIF*-mediated signaling, which is caused by hyperglycemia and increased fatty acid levels , which suppress *HIF-1α* stability and activity[12]. Chronic hypoxia is implicated in multiple physiological processes , such as diabetes. At the molecular level, hypoxia signaling occurs through the activation of HIF-dependent gene transcription [13].

The results of the present research observed a marked elevate in expression level of *HIF-1α*in diabetes patient in compared with control group, this result align closely with previous **,** in agreement with [15] indicated that the hypoxia condition stimulated the upregulation of *HIF-1α* in cells cultured under high glucose environment compared to those exposed to normal levels of glucose , and with [16] noted that the context of diabetic and hypoxia conditions, elevated glucose suppresses *HIF-1 a*in the kidney through a proly l-hydroxylase-mediated pathway. Conversely, some suggest that excessive glucose conditions significantly reduced the expression level of HIF-1α [14] .

Our results revealed that *p53* expression was significantly higher in diabetic patients than in the control group, which agrees with previous data suggesting that a different association between the p53 codon polymorphism had a distinct implication in type 2 diabetes and related complications, possibly due to its involvement in mitochondrial DNA maintenance under hyperglycemic conditions [17]. Several investigations have highlighted the role of *p53* in diabetes, for example, in animal models fed a high-fat diet, metabolic stress activates *p53*, leading to the induction of insulin resistance and cellular senescence. Despite this, several studies have demonstrated conflicting results associated with diabetes. Many studies have indicated that *p53* activation can either participate in the progression of diabetes, while others suggested their effect in suppressing the diabetic progression [18]; [19]; [20]; [21].

The present study investigated the effects of diabetes, gender, and IBM on *HIF-1α* and *p53* gene expression after adjusting for a covariate. Although no significant main effects were observed, a borderline interaction between diabetes and gender suggests that the influence of diabetes on *HIF-1α* does not differ between males and females, while *p53* expression may differ between males and females. The adjusted marginal means illustrated in this observation show divergent trends in *p53* expression between male and female participants across diabetes status. This pattern suggests a possible sex-dependent modulation of *p53*-related pathways in the context of diabetes,[22] these results suggested that the prevalence of T2DM is rising in both sexes, but male are generally identified as a younger age and lower level of total fat mass than their female, while [23] indicated that there was no evidence of a stable pattern of sex differences in relation to glucose metabolism status and glycemic outcomes**.** [24] reported that a broad-scale candidate gene study identified a

significant association between susceptibility for T2DM and a common functional polymorphism of *p53*.

The prevalence of T2DM continues to rise dramatically, and substantial evidence suggests that *p53* plays a key role in metabolic homeostasis, particularly in regulating lipid and glucose metabolism [25] .

Our study also observed a significant and strong positive correlation between gene expression of HIF-1α and p53. These findings support the functional role of hypoxia-related signaling (*HIF-1α*)in regulating cellular senescence through the activation of *p*53-mediated pathway in the studied samples, [13] indicating that *p53*controls multiple biological functions and interacts with HIF-1α in a complex manner, and has a complex influence in the regulation of cellular responses to hypoxia.[9]Also referred to as the hyperglycemia-triggered disruption of *HIF-α* mediated signaling through activation of *p53*, thereby implicating the *p53* signaling pathway as a potential target in diabetes therapy

[26] Showed that under specific conditions, such as transient hypoxia, *p53* could promote cell survival through the activation of adaptive signaling pathways. However, during more severe or prolonged hypoxia stress, it may act in cooperation with *HIF1* to modulate cellular responses. Extensive hypoxic stress triggers *p*53 accumulation, a key mediator of inducing cell death and tissue injury under low oxygen conditions [27]

The finding suggested that both hyperglycemia and diabetes interfere with the *HIF-α1 signaling*-mediated pathway and alter the metabolism of cells through upregulation of p53. Under high glucose, the expression level of *p53* was increased, leading to further investigation of the potential molecular mechanisms through which hyperglycemia promotes *HIF-α* signaling and enhances oxygen uptake rate in the cardiomyocytes [9] . An in vitro study using the SH-SY5Y cell model demonstrated that hyperglycemia induced apoptosis and was accompanied by an elevated acetylation of *p53* [28]. Also, [29] confirmed that suppression of *p53* has significantly reduced cellular senescence during the early stage of diabetes, attenuated diabetes-promoted senescence of the cell during disease progression, and improved angiogenic and glycolytic deficiencies by elevating *HIF-1α* protein stability and activation of its downstream target genes. [30] provide new evidence implicating the *HIF-1α* signaling pathway in inflammation triggered by high glucose and hypoxia . This pathway may act as a novel regulator of inflammation-related processes in response to diabetic injury and may be impacted in the progression and development of diabetes.

Conclusion

In conclusion, our study revealed a significant upregulation of *HIF-1α* and *p53* gene expression in the patient group compared with controls, suggesting their potential involvement in disease-related molecular mechanisms. The overall covariance models were statistically significant; however, diabetes status, gender, and body mass index were not independent

predictors of the expression levels of either gene. Notably, a significant positive correlation between *HIF-1α* and *p53* expression suggests a possible coordinated regulatory relationship between hypoxia-related and apoptosis pathways. Additionally, all of these results support the essential role of *(HIF-1α* and *p53*) as interconnected molecular markers and warrant further large-scale and mechanistic studies. More research is needed to enhance our understanding of the fundamental involvement of *HIF-1α* and *p53* in the progression of diabetes.

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نقص الاكسجة يحفيز موت الخلايا المبرمج في خلايا الدم بواسطة تفعيل بروتين P53 لدى مرضى السكري

ازهر امين وجماعته

فرط سكر الدم في مرض السكري يعزز نقص الأكسجة، مما يؤدي إلى تغييرات في البيئة الدقيقة للخلايا اذ يعمل نقص الأكسجة على تحفيز استجابات خلوية ، والتي يتم تنظيمها بشكل كبير عن طريق عامل نسخي يُعرف باسم عامل نقص الأكسجة القابل للتحفيز 1-ألفا (*HIF-1α*). بالإضافة إلى ذلك، يؤثر نقص الأكسجة على تفعيل مسارات موت الخلايا من خلال تثبيت عامل مثبط الأورام p53. تهدف الدراسة الحالية إلى تقييم دور التعبير الجيني لعامل نقص الأكسجة القابل للتحفيز (*HIF-1α*) في تنظيم إشارة p53 لدى الأفراد المصابين بمرض السكري من النوع الثاني (T2DM) مقارنةً بالمجموعة الضابطة غير المصابة بمرض السكري. تم الحصول على عينات الدم الكامل من كل من المشاركين المصابين بمرض السكري من النوع الثاني وغير المصابين، تلا ذلك استخدام تقنية PCR الكمي (qPCR) لتقدير مستويات التعبير الجيني لكل من (*HIF-1α* و*P53*). أظهرت النتائج زيادة كبيرة في التعبير الجيني لكل من (HIF-1α وP53) لدى المرضى مقارنةً بالمجموعة الضابطة. و كذلك أظهر تحليل التباين المشترك أن النماذج الإجمالية لتعبير (*HIF-1α* و*P53*) كانت ذات دلالة إحصائية، في حين لم تظهر متغيرات السكري، الجنس، ومؤشر كتلة الجسم (BMI) تأثيرات مستقلة ذات دلالة , بالإضافة إلى ذلك، تم الكشف عن ارتباط إيجابي ملحوظ بين تعبير كل من (*HIF-1α* و*P53*).استنتجت الدراسة الحالية انه ل

HIF-1α تأثير محتمل في تحفيز موت الخلايا المبرمج من خلال زيادة التعبير عن *p53* وبالتالي، توفر هذه النتائج دليلاً على أن *HIF-1α* و *p53* يمكن أن يعملان كعلامات خلوية مترابطة، لذا يتوجب إجراء المزيد من الدراسات على مجموعات اوسع من المشاركين.

الكلمات المفتاحية :

موت الخلايا المبرمج , فرط سكر الدم , البيئة الدقيقة للدم , داء السكري نوع , عامل نقص الاكسجة للتحفيز الفا-1