

# Association of plasma hypoxia-inducible factor-1 alpha in severely obese individuals with type 2 diabetes

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## 1. Introduction

- Obesity and type 2 diabetes (T2D) are often attributed to hypoxia.
- Hypoxia-inducible factor (HIF)-1 $\alpha$  is regulated in response to hypoxia and induces the expression of target genes involved in diverse physiological and pathological processes.
- The role of hyperglycemia in the regulation of HIF-1 $\alpha$  expression and activity still remains unclear.

**Aim:** This cross-sectional study aimed to evaluate the association between plasma HIF-1 $\alpha$  and T2D in the severely obese individuals.

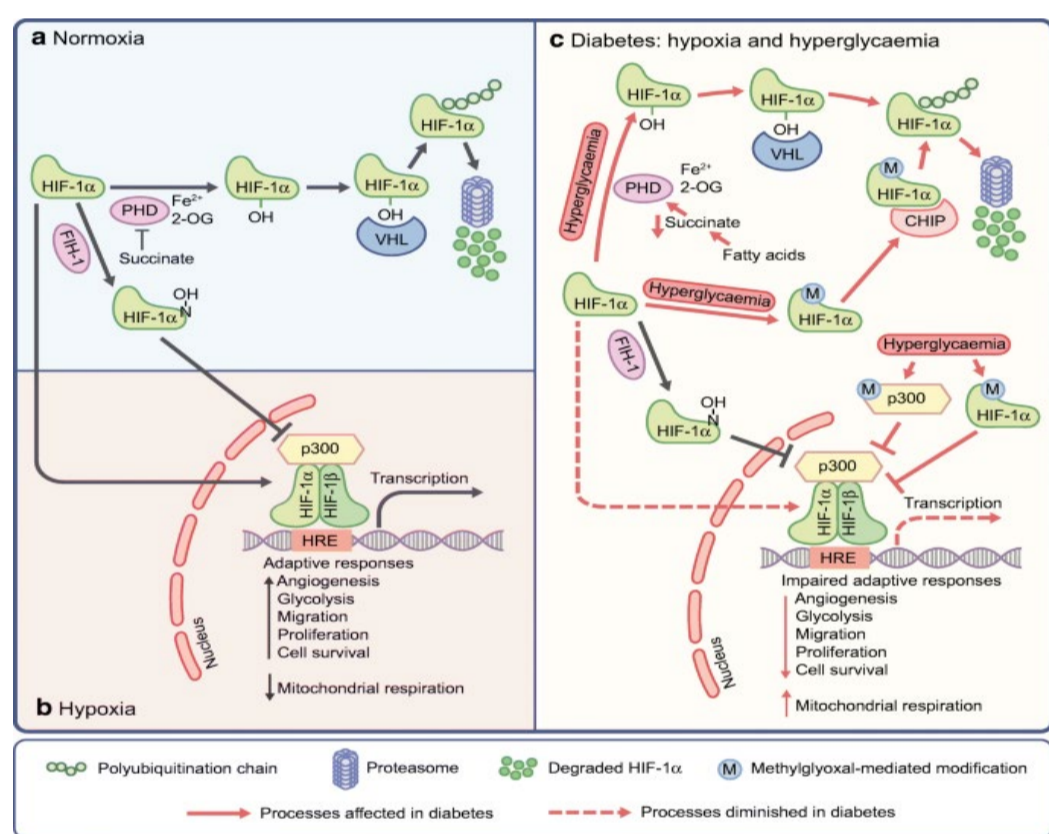


Figure 1 This figure shows the regulation of hypoxia inducible factors under diabetic and non-diabetic conditions. Reference: Catrina, SB., Zheng, X. Hypoxia and hypoxia-inducible factors in diabetes and its complications. *Diabetologia* **64**, 709–716 (2021). <https://doi.org/10.1007/s00125-021-05380-z>

## 2. Methods

The study involved adults with severe obesity recruited into Obesity-Metabolism Intervention Cohort Study between 2007 to 2019.

The levels of HIF-1 $\alpha$  in the plasma were measured by immunoassay.

The association of HIF-1 $\alpha$  levels with HbA1c and T2D in severely obese individuals was assessed using Spearman's correlation and modified Poisson regression analysis.

## 3. Results

Table 1 Baseline characteristics of the study participants

Variables (N=252)	Non-T2D (N=121)	T2D (N=131)	P value
Age (years)	45 $\pm$ 7	46 $\pm$ 9	<b>0.031</b>
Gender, n (%)			<b>0.000</b>
Female	86 (71)	71 (54)	
Male	35 (29)	60 (46)	
BMI (kg/m <sup>2</sup> )	41.6 $\pm$ 6.3	40.6 $\pm$ 6.7	0.520
HbA1c %	5.87 $\pm$ 0.4	8.51 $\pm$ 1.9	<b>0.000</b>

BMI: Body mass Index; HbA1c: Glycated haemoglobin

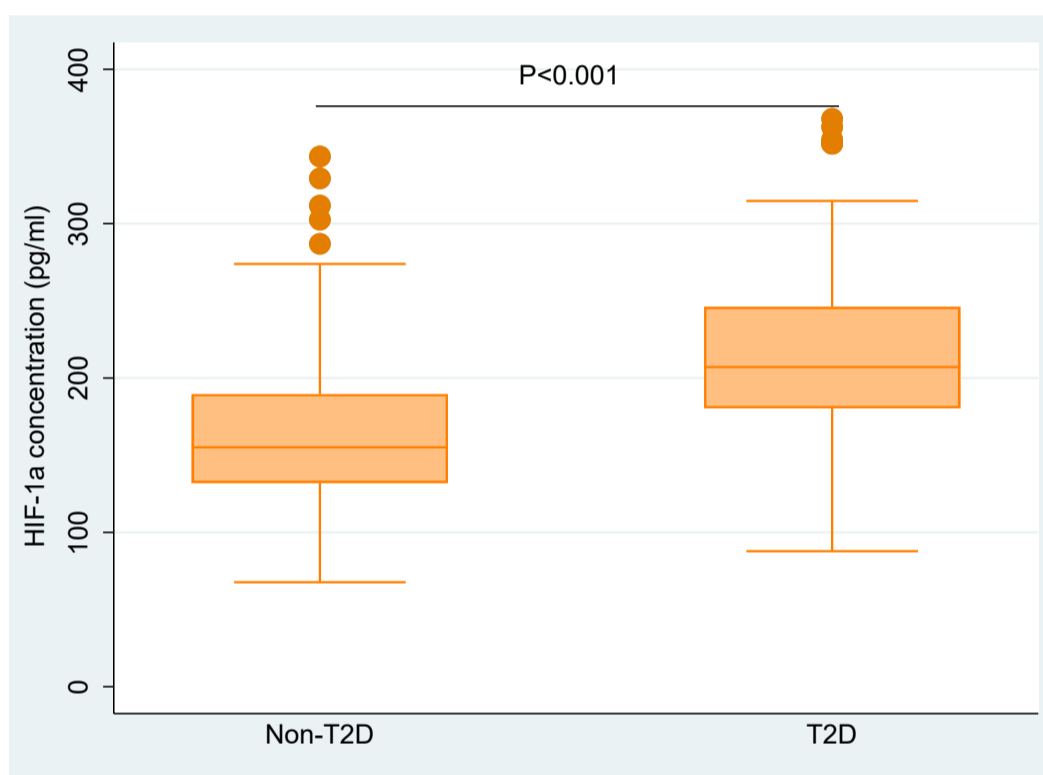


Figure 2 Box plot shows that individuals with T2D displayed higher median HIF-1 $\alpha$  levels compared with individuals without T2D [207.1 (interquartile range:180.4–246.1) vs 155.1 (interquartile range:132.0–189.6) pg/ml;  $P < 0.001$ ]

A positive correlation was observed between HIF-1 $\alpha$  levels in the plasma and HbA1c % ( $\rho = 0.295$ ,  $P < 0.001$ ).

Table 2 Univariable and multivariable linear regression analysis of factors associated with natural log-transformed HIF-1 $\alpha$  and T2D (outcome)

Variables	Risk Ratio (95% CI)*	P value*	Risk Ratio (95% CI) †	P value †
Age (years)	1.00 (0.99-1.02)	0.484	1.00 (0.99-1.01)	0.457
Gender	1.39 (1.11-1.76)	0.005	1.28 (1.07-1.53)	0.007
BMI (kg/m <sup>2</sup> )	0.99 (0.97-1.00)	0.238	0.99 (0.98-1.00)	0.460
HbA1c %	1.23 (1.18-1.29)	0.000	1.20 (1.15-1.26)	0.000
lnHIF-1 $\alpha$	4.24 (2.93-6.15)	0.000	2.63 (1.85-3.73)	0.000
Constant	NA	NA	0.00	0.000

\*Estimates were derived from univariable analysis  
 † Estimates were derived from multivariable analysis containing all five variables listed in column 1  
 CI: Confidence Interval; lnHIF-1 $\alpha$ : Natural log-transformed HIF-1 $\alpha$ .

## 4. Conclusion

Notably, HIF-1 $\alpha$  is higher in severely obese individuals with type 2 diabetes compared to the non-T2D counterparts. Further, our data suggest that hyperglycemia may result in the accumulation of HIF-1 $\alpha$  protein, which could contribute to the development of T2D-associated complications. Hence, inhibition of HIF-1 $\alpha$  expression may exert beneficial effects on T2D and its complications.