Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2020 Apr 10; 8(B):408-413.
https://doi.org/10.3889/oamjms.2020.3926
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Endocrinology*

Correlation of Hypoxia-Inducible Factor-1α Level with Control Glycemic in Type 2 Mellitus Patients with Malignancy and Without Malignancy

Rusdiana Rusdiana[1]*, Maya Savira[2], Kamal Basri Siregar[3], Sry Suryani Widjaja[1], Dedi Ardinata[2]

[1]Department of Biochemistry, Medical Faculty, Universitas Sumatera Utara, Jl. Dr. Mansur No. 5, Medan, Indonesia; [2]Department of Physiology, Medical Faculty, Universitas Sumatera Utara, Jl. Dr. Mansur No.5, Medan, Indonesia; [3]Department of Surgery, Oncology Subdivision, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Rusdiana R, Savira M, Siregar KB, Widjaja SS, Ardinata D. Correlation of Hypoxia-Inducible Factor-1α Level with Control Glycemic in Type 2 Mellitus Patients with Malignancy and Without Malignancy. Open Access Maced J Med Sci. 2020 Apr 10; 8(B):408-413. https://doi.org/10.3889/oamjms.2020.3926
Keywords: Diabetes mellitus Type 2; Malignancy; Fasting blood sugar; HbA1c; Hypoxia-inducible factor 1-alpha
***Correspondence:** Rusdiana Rusdiana, Department of Biochemistry, Medical Faculty, Universitas Sumatera Utara, Jl. Dr. Mansur No. 5, Medan, Indonesia.
E-mail: rusdiana@usu.ac.id
Received: 28-Oct-2019
Revised: 09-Feb-2020
Accepted: 06-Mar-2020

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Type 2 diabetes mellitus (T2DM) is becoming increasingly prevalent worldwide. Malignancy is one of the most common causes of death in the world. T2DM is one of the risk factors for malignancy. This is caused by an increase in blood glucose levels (hyperglycemia) which will cause tissue hypoxia which can lead to malignancy. The cell adaptation response to hypoxia is relaxed by a marker called hypoxia-inducible factor-1 alpha (HIF-1α), where a condition converts hyperglycemia to a loss of cellular response to hypoxia in most complications of diabetes.

AIM: The aim of this study was to determine level HIF-1α at T2DM with malignancy, where this study used the samples of the T2DM patients with malignancy and T2DM without malignancy.

METHODS: The cross-sectional study design used the 89 samples of DM patients with and without malignancy who attended Murni Teguh Hospital in Medan of Indonesia country. The inclusion criteria of the samples were all the patients diagnosed with T2DM with or without malignancy, both the sexes. Body mass index, blood pressure, disease history, and socioeconomic status were recorded. The laboratory parameters, including fasting blood sugar (FBS) and HbA1c, were examined by Murni Teguh Hospital Laboratory and HIF-1α; we examined by ELISA methods in the laboratory Medical Faculty, Sumatera Utara Universitas.

RESULTS: In this study, we found that there was no significant correlation between HIF-1α with FBS and HbA1c ($p > 0.005$), but we found that there was a significant correlation HbA1c with FBS ($p < 0.005$).

CONCLUSION: The results of the study revealed HIF-1α at the both of the group of the samples even in the relative small amounts until a large amounts in the serum, but we found that there was no correlation significantly between HIF-1α and glycemic index (HbA1c and FBS), while there was correlation significantly between Hba1c and FBS.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease caused by the body's inability to produce insulin hormone as needed or due to the ineffective use of insulin or both. This is characterized by high blood sugar levels (hyperglycemia). At present, there is an increase in the prevalence of DM throughout the world. DM is known as a key factor contributing to the development of malignancies from solid organs, including the liver, pancreas, rectal colon, breast, endometrium, uterus, and bladder [1]. In 2013, there were 382 million people in the world aged 40–59 years suffering from DM, and it is estimated that it will continue to increase every year. Regional International Diabetes Federation data show that Southeast Asia is ranked the second-highest in the world with a total DM population of 72 million. In 2035, it is estimated that this figure will increase by 70.6% to 122.8 million; this increase in the prevalence of DM occurs throughout the world in both developed and developing countries [2], [3].

The number of diabetics in Indonesia is ranked 7th in the world. At present, the prevalence of diabetes in Indonesia, which doctors have diagnosed, is 1.4%, this number is expected to continue to increase (Riskesdas, 2013). The WHO estimates that 21,527,000 Indonesians will suffer from DM by 2030 [4]. DM is characterized by defects in hypoxia-induced neovascularization in the myocardium, skeletal muscle, nerves, and skin. Inadequate collateral vessel formation in response to ischemia increases cardiovascular morbidity and mortality in diabetic patients [5]. DM and malignancy are frequently diagnosed in the same individual [6]. The mechanism for the diabetes-cancer link has been hypothesized to be mainly related to hormonal insulin and insulin-like growth factor (IGF)-1, inflammatory, or metabolic (hyperglycemia) characteristics of the DM and even to certain treatments [7]. Antidiabetic medications may have effects on the risk of cancer. Many studies found that diabetes was consistently related to increased risk for a broad variety of malignancies, and the prospective researches reported that there was a relation of increased blood glucose with

increased overall cancer incidence and that postulated as a linear trend of increased blood glucose levels and cancer risks [8]. Several large cohort and case–control studies have found a positive relationship between hyperglycemia and the risk of cancer [9] and the other researches that a meta-analysis comprising 30 cohort studies showed that diabetes was associated with an increase in the risk of colorectal cancer [10], [11].

Cancer occurs in a condition, where the cell has lost its normal control and mechanism, resulting in abnormal growth [12]. Although the science is increasingly sophisticated, until now, it is not known with certainty the main cause of breast cancer, which is estimated to be very multifactorial [13]. Diabetes with malignancy is a common disease with extraordinary health impacts throughout the world [14]. Epidemiological evidence showed that people with diabetes have a significantly higher risk of developing malignancy [15]. Type 2 diabetes mellitus (T2DM) and malignancy have many risk factors, but the potential biological relationship between the two diseases is not fully understood. Moreover, evidence from observational studies showed that some drugs used to treat hyperglycemia are associated with an increase or decrease in cancer risk; [16] there are a variety of antidiabetic interventions, including sulfonylureas, α-glucosidase inhibitors, biguanides, and thiazolidinediones (TZDs) [17] that increase the level of circulating insulin, thereby reducing hyperglycemia by various mechanisms. Metformin inhibits cell proliferation and induces apoptosis in cancer cell lines [18], whereas metformin and other biguanides decrease the cancer incidence [19] that some confounding factors are directly related to the clinical diversity of diabetes levels at the level of metabolic control, duration of diabetes, antidiabetic therapy profile, and the presence of complications or comorbidities [19]. A number of the factors that contribute to the increased risk of developing cancer in T2DM include hyperglycemia, insulin resistance, hyperinsulinemia, increased levels of IGF-1, dyslipidemia, cytokines, increased leptin, and decreased levels of adiponectin [20], [21], [22].

Recently, many studies improved that DM is often associated with hypoxia which damages induced neovascularization during the process of ischemia and other forms of cell response and adaptive tissue to low oxygen levels [23]. Hyperglycemia seems to be the driving force for such deregulation. Recent data on destabilization of hypoxia-inducible factor-1-alpha (HIF-1α) are likely to be events that hyperglycemia loss cellular response to hypoxia in most diabetes complications [24]. HIF-1α was a master regulator that mediates the cellular response to hypoxia [25] so that has been proven that HIF-1α plays a role in the pathogenesis of malignancy too. Due to that, this aim study wants to know how the correlation about the HIF-1α with the control glycemic in type 2 mellitus patients with malignancy and without malignancy.

Materials and Methods

Subjects

We included 89 of the samples, consecutive T2DM with malignancy and T2DM without malignancy, between January and July 2019, who attended to Murni Teguh Hospital in Medan, North Sumatera, Indonesia, according to ADA and the WHO guidelines. The samples was composed of all T2DM with or without malignancy, both male and female, without the exception the age and treatment. Exclusion criteria were type 1 DM and severe disease. Physical examinations were performed to record patient demographics, including height, weight, body mass index (BMI), and blood pressure. Biochemical tests were done as fasting blood sugar (FBS) and HbA1c. All participants were provided written informed consent at the visits and explain of the examination for the samples and this study was in compliance with the Declaration of Helsinki. Our study was approved by our Institutional Health Research Ethics Committee with number 484/TGL/KEPK FK USU-RSUP HAM 2019.

Biochemical measurements

Before the blood samples were collected at a visit to the outpatient clinic, the samples must fast overnight. The blood of the samples was centrifuged at 3000 rpm at 4°C for 15 min. The supernatants were decanted and frozen at −80°C until assayed. FBS and HbA1c were measured using standard methods. FBS was examined by the machinery portable measuring instrument (Gluco DR) and HbA1c was measured by the HPLC method. The plate has been pre-coated with human HIF-1α antibody. HIF-1α presents in the sample is added and binds to antibodies coated on the wells instead use then biotinylated human HIF-1α. The antibody is added and binds to HIF-1α in the sample. The substrate solution is then added, and color develops in proportion to the amount of human HIF-1α. The reaction is terminated by the addition of acidic stop solution, and absorbance is measured at 450 nm. Intra-assay and inter-assay coefficients of variation for HIF-1α were <8% and <10%, respectively.

Statistical analysis

SPSS version 24.0 (SPSS Inc., Chicago, Illinois) statistical software was used for statistical analysis. All the variables in this sample of the study were tested by Shapiro–Wilk, the normal distribution variables ($p > 0.005$) were tested by parametric correlation test, but the abnormal distribution variables ($p < 0.005$) were tested by non-parametric test.

Results

All the subjects of this study 89 samples, average 38–77 years old, consist of 36 males (40.4%) and 53 females (59.6%). The subjects of this study were 40 samples with T2DM with malignancy and 49 samples without malignancy. The characteristics of the subjects of the study are included in Tables 1 and 2, BMI of the Group 1 was 24.89 ± 4.59 kg/m^2 that subjects were normal and preobese group; according to the WHO, the BMI of the subjects at the samples with T2DM without malignancy was 25.78 ± 4.59 kg/m^2 that subjects were a normal and preobese group.

Table 1. Characteristic of samples of diabetes mellitus Type 2 with malignancy (group 1) (n=40)

Parameter	Minimum	Maximum	Mean	SD
Age (years)	37	73	56.90	8.75
BMI (kg/m^2)	19.53	37.78	24.89	4.59
FBS (mg/dl)	83	635	260.45	105.55
Hba1c (%)	2.4	12.70	7.57	2.26
HIF-1α (ng/ml)	0.0	17.80	1.67	3.73

The minimum of the FBS levels in the subjects with T2DM with malignancy was 83 mg/dl and the maximum was 635 mg/dl and the minimum of the FBS levels of the subjects with T2DM without malignancy was 87 mg/dl and the maximum of the FBS levels was 500 mg/dl. In the both of the samples group we found average hyperglycemia. The mean of the HbA1c value in the subjects of type DM with malignancy was 7.57 ± 2.26% which should be good and the bad level of the glycemic control. However, the mean of the HbA1c of the subject of T2DM without malignancy was 9.34 ± 1.62% which means that all the subjects had bad glycemic control. T2DM with malignancy found the HIF-1α in relative small (0.000) accounts in the plasma until the high concentration of HIF-1α (17.80 ng/ml). In the samples of T2DM without malignancy we found relative small HIF-1α levels in the plasma (0.00) and the highest of the HIF-1α levels in the plasma (3.16 ng/mL). All the subjects were found that the HIF-1α levels were highest at the subjects of DM with malignancy. But by statistics, we found that there was no significant difference between HIF-1α at the subjects at T2DM with malignancy without malignancy (p = 0.005).

Table 2. Characteristic of samples of diabetes mellitus type 2 without malignancy (group 2) (n=49)

Parameter	Minimum	Maximum	Mean	SD
Age (years)	38	77	59.31	8.1
BMI (kg/m^2)	18.55	41.84	25.78	4.59
FBS (mg/dL)	87	500	229.76	89.46
Hba1c (%)	6.10	14	9.34	1.62
HIF-1α (ng/mL)	0.0	3.16	0.69	0.84

Non-parametric correlation		
Correlations	HIF-1α	Hba1c
Spearman's rho		
HIF-1α		
Correlation coefficient	1.000	–0.111
Sig. (two-tailed)	-	0.301
N	89	89
Hba1c		
Correlation coefficient	–0.111	1.000
Sig. (two-tailed)	0.301	-
N	89	89

Parametric correlation		
Correlations	FBS	Hba1c
Spearman's rho		
FBS		
Correlation coefficient	1.000	0.292**
Sig. (two-tailed)	-	0.005
N	89	89
Hba1c		
Correlation coefficient	0.292**	1.000
Sig. (two-tailed)	0.005	-
N	89	89

**Correlation is significant at the 0.01 level (two-tailed).

In this study, we found that there was no significant correlation between HIF-1α with FBS and HbA1c (p > 0.005), but we found that there was a significant correlation HbA1c with FBS (p < 0.005).

Discussion

Hyperglycemia was the characteristic of T2DM, and the previous studies with T2DM it was found increasing HIF-1α levels, indicated a state of the severity of DM [26]. T2DM with retinopathy was associated with the increased plasma HIF-1α levels and indicate that diabetic retinopathy will occur in the future and at the advanced retinopathy, because the average HIF-1α level was higher than that of the mild retinopathy group. Low or normal plasma HIF-1a levels depended on the degree of diabetic retinopathy [27]. HIF-1α levels do not have a relationship with microalbuminuria and interactions with microalbuminuria with retinopathy [28]. Research by Zhang *et al*. said that hyperglycemia was significantly increasing HIF-1α [29]. Other studies showed that hyperglycemia and hypoxia were suspected to play a role in the pathophysiology of DM complications, due to the defective response of cells to low oxygen pressure [30]. Research by Sergiu-Bog and Catrina *et al*. said that primarily endothelial cells and dermal fibroblasts, hyperglycemia interferes with the function of induced hypoxia factor-1 alpha, which is a transcriptional factor in response to cell adaptation to the hypoxia process [31]. The occurrence of hypoxia is due to inadequate perfusion in adipose that has hyperplasia or hypertrophy. DM has a higher risk of malignancy compared to populations that do not have diabetes. Diabetes the risk of the some malignancies and also the negative prognosis affects people with DM after the diagnosed [32]. Patients with diabetes have a higher risk than the population without diabetes to suffer from cancer of the urinary tract, liver, bile ducts, pancreas, colon, endometrium, and kidneys [33], [34].

Long before HIF-1α was discovered in 1927 by Warburg *et al*. the observation that a malignancy occurred that produce high levels of lactate even in the presence of abundant oxygen [35]; he attributed this unusual form of aerobic glycolysis to mitochondrial injury. This glycolytic shift has been observed in dozens of cancers where rates of glycolysis may be 200 times higher than in non-cancer cells [36]. The

previous studies found that hypoxia activated HIF-1α which results in the control of the post-ischemia revascularization process [37]. Recent research has revealed that destabilization of HIF-1α was most likely an event that transduced that hyperglycemia into a loss of cellular response to hypoxia in most diabetic complications [38]. HIF-1α levels decrease on biopsy of foot ulcers in patients with DM compared to venous ulcers that have the same hypoxic environment, but are not exposed to hyperglycemia. Decreased regulation of HIF-1α in response to hyperglycemia also appears to be responsible for the decrease in collateral growth triggered by myocardial ischemia in patients with DM [35]. Research by Jiang et al. found that a significantly increased HIF-1α levels in diabetics who were carried out in a cohort study, and followed by increased of the vascular endothelial growth factor (VEGF) [11]. This study also showed a positive correlation between serum VEGF and HIF-1α in patients with DM, presumably due to extensive HIF-1α role in regulating VEGF expression in diabetes. It was shown that HIF-1α, as a master regulator of cell response to hypoxic stress, plays important roles in breast cancer metastasis too [39]. We reported in this study this point of view by demonstrating that hypoxia/HIF-1 induces cancer stem-like cells by Jagged2 or mediates paracrine signaling between breast cancer cells and mesenchymal stem cells to promote metastasis [40]. However, this study did not show a significant correlation between HIF-1α with HbA1c or with FBS ($p > 0.005$). However, the results showed a significant correlation between HbA1c and FBS ($p < 0.005$), where $r^2 = 0.087$, where FBS affected HbA1c 8.7%, and the rest was influenced by other factors. However, almost all samples of the study were found to have HIF-1α levels with different concentration levels, where the presence of HIF-1α was indicated the presence of hypoxic areas. In our study, we only classified the samples in two groups of Type 2 DM - with malignancy and without malignancy. However, both groups showed the levels of HIF-1α with different concentrations with the minimum values in the groups being the same, but the maximum values in the two groups were very different, where the maximum values in the T2DM group were much higher than those in the DM group without malignancy [41], [42].

Conclusion

It can be concluded that high levels of HIF-1α in DM samples with malignancy indicate the severity of the disease and the malignancy process suffered by the sample due to the ongoing hypoxia process. In spite of the high levels of the DM group without malignancy, we cannot conclude that they will experience a malignancy process, as well as there are still many factors involved. The higher levels of HIF-1α from the samples will experience a higher risk of getting a disease complication compared to the HIF-level with low 1α.

Acknowledgments

The authors gratefully acknowledge that the present research is supported by the Ministry of Research and Technology and Higher Education Republic, Indonesia. The support is under the research grant TALENTA USU of the year 2019.

References

1. Kulie T, Slattengren A, Redmer J, Counts H, Eglash A, Schrager S. Obesity and women's health: an evidence-based review. J Am Board Fam Med. 2011;24(1):75-85. https://doi.org/10.3122/jabfm.2011.01.100076
   PMid:21209347
2. American Diabetes Association. Diagnosis and Classification of diabetes Mellitus. New York: American Diabetes Association; 2009.
3. Republik Indonesia. Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan. Jakarta, Indonesia: Republik Indonesia; 2013.
4. International Diabetes Federation. Riset Kesehatan Dasar Jakarta. F Diabetes Atlas. International Diabetes Federation; 2013. Available from: http://www.idf.org/diabetesatlas. [Last accessed on 2019 Mar 10].
5. Martin A, Komada MR, Sane DC. Abnormal angiogenesis in diabetes mellitus. Med Res Rev. 2003;23(2):117-45. https://doi.org/10.1002/med.10024
   PMid:12500286
6. Onitilo AA, Engel JM, Glurich I, Stankowski RV, Williams GM, Doi SA. Diabetes and cancer I: Risk, survival, and implications for screening. Cancer Causes Control. 2012;23(6):967-81. https://doi.org/10.1007/s10552-012-9972-3
   PMid:22552844
7. García-Jiménez C, García-Martínez JM, Chocarro-Calvo A, De la Vieja A. A new link between diabetes and cancer: Enhanced WNT/β-catenin signaling by high glucose. J Mol Endocrinol. 2014;52(1):R51-66. https://doi.org/10.1530/jme-13-0152
   PMid:24049067
8. Stocks T, Rapp K, Bjørge T, Manjer J, Ulmer H, Selmer R, *et al*. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (Me-Can): Analysis of six prospective cohorts. PLoS Med. 2009;6(12):e1000201. https://doi.org/10.1371/journal.pmed.1000201
   PMid:20027213
9. Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schünemann HJ, *et al*. Fasting glucose is a risk factor for breast cancer: A prospective study. Cancer Epidemiol Biomarkers Prev. 2002;11:1361-8.
   PMid:12433712
10. Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL,

Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiol Biomarkers Prev. 2003;12(5):412-8.
PMid:12750235

11. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: A systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26(11):863-76. https://doi.org/10.1007/s10654-011-9617-y
PMid:21938478
12. Noto H, Tsujimoto T, Sasazuki T, Noda M. Significantly increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis. Endocr Pract. 2011;17(4):616-28. https://doi.org/10.4158/ep10357.ra
PMid:21454235
13. Min H, Kornelia P. Microenvironmental regulation of cancer development. Curr Opin Genet Dev. 2008;18(1):27-34. https://doi.org/10.1016/j.gde.2007.12.006
14. Pernicova I, Korbonits M. Metformin: Mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014;10(3):143-56. https://doi.org/10.1038/nrendo.2013.256
PMid:24393785
15. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care. 2010;33:1304-8. https://doi.org/10.2337/dc09-1791
PMid:20299480
16. Krentz AJ, Bailey CJ. Oral antidiabetic agents: Current role in Type 2 diabetes mellitus. Drugs. 2005;65:385-411. https://doi.org/10.2165/00003495-200565030-00005
PMid:15669880
17. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with Type 2 diabetes: Systematic review. PLoS One. 2013;8:e71583. https://doi.org/10.1371/journal.pone.0071583
PMid:23936520
18. Zordoky BN, Bark D, Soltys CL, Sung MM, Dyck JR. The anti-proliferative effect of metformin in triple-negative MDA-MB-231 breast cancer cells is highly dependent on glucose concentration: implications for cancer therapy and prevention. Biochim Biophys Acta. 2014;1840(6):1943-57. https://doi.org/10.1016/j.bbagen.2014.01.023
PMid:24462945
19. Ece H, Cigdem E, Yuksel K, Ahmet D, Hakan E, Oktay TM. Use of oral antidiabetic drugs (Metformin and Pioglitazone) in diabetic patients with breast cancer: How does it effect on serum Hif-1 alpha and 8Ohdg levels? Asian Pac J Cancer Prev. 2012;13(10):5143-8. https://doi.org/10.7314/apjcp.2012.13.10.5143
PMid:23244125
20. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: A review of the evidence. J Nutr. 2001;131(11 Suppl):3109S-20S. https://doi.org/10.1093/jn/131.11.3109s
PMid:11694656
21. Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res. 2009;69(19):7507-11. https://doi.org/10.1158/0008-5472.can-09-2994
PMid:19752085
22. Mcpherson K, Steel CM, Dixon JM. 5 Breast cancer epidemiology, risk factors, and genetics. ABC of Breast Dis. 2009;572:24.
23. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, *et al*. Diabetes and cancer: A consensus report. CA Cancer J Clin. 2010;60(4):207-21.
PMid:20554718
24. Katherine LT, Turley H, Gatter KC, Maxwell PH, Pugh CW, Ratcliffe PJ, *et al*. The expression and distribution of the hypoxia-inducible factors HIF-1α and HIF-2α in normal human tissues, cancers, and tumor-associated macrophages. Am J Pathol. 2000;157(2):411-21. https://doi.org/10.1016/s0002-9440(10)64554-3
PMid:10934146
25. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with Type 1 and Type 2 diabetes: Disentangling true associations, detection bias, and reverse causation. Diabetes Care. 2015;38(2):264-70. https://doi.org/10.2337/dc14-1996
PMid:25488912
26. Li QF, Xu H, Sun Y, Hu R, Jiang H Induction of inducible nitric oxide synthase by isoflurane post-conditioning via hypoxia inducible factor1aduring tolerance against ischemic neuronal injury. Brain Res. 2012;1451:1-9. https://doi.org/10.1016/j.brainres.2012.02.055
PMid:22445062
27. Thangarajah H, Yao D, Chang EI, Shi Y, Jazayeri L, Vial IN, *et al*. The molecular basis for impaired hypoxia-induced VEGF expression in diabetic tissues. Proc Natl Acad Sci USA. 2009;106(32):13505-1. https://doi.org/10.1073/pnas.0906670106
PMid:19666581
28. Hoo Y, Mahmoud AA. Hypoxia inducible factor-1α in Type 2 diabetes mellitus with microalbuminuria and retinopathy. Majalah Kedokt Bandung Bandung Med J. 2014;46(2):100-5. https://doi.org/10.15395/mkb.v46n2.281.
29. Lin M, Chen Y, Jin J, Hu Y, Zhou KK, Le YZ, *et al*. Ischaemia-induced retinal neovascularisation and diabetic retinopathy in mice with conditional knockout of hypoxia-inducible factor-1 in retinal Muller cells. Diabetologia. 2011;54(6):1554-66. https://doi.org/10.1007/s00125-011-2081-0
PMid:21360191
30. Liang J, Qian Y, Xu D, Yin Q, Pan HJ. Serum tumor markers: Hypoxiainducible factor-1α HIF-1α and vascular endothelial growth factor, in patients with non-small cell lung cancer before and after intervention. Asian Pac J Cancer Prev. 2013;14(6):3851-4. https://doi.org/10.7314/apjcp.2013.14.6.3851
PMid:23886195
31. Zhang Z, Yan J, Shi H. Role of hypoxia inducible factor 1 in hyperglycemia exacerbated blood-brain barrier disruption in ischemic stroke. HHS Public Access. 2016;95:82-9. https://doi.org/10.1016/j.nbd.2016.07.012
PMid:27425889
32. Bento CF, Pereira P. Regulation of hypoxia-inducible factor 1 and the loss of the cellular response to hypoxia in diabetes. Diabetologia. 2011;54:1946-56. https://doi.org/10.1007/s00125-011-2191-8
PMid:21614571
33. Catrina SB, Okamoto K, Pereira T, Brismar K, Poellinger L. Hyperglycemia regulates hypoxia-inducible factor-1alpha protein stability and function. Diabetes. 2004;53(12):3226-32. https://doi.org/10.2337/diabetes.53.12.3226
PMid:15561954
34. Scheid A, Wenger RH, Schaffer L, Camenisch I, Distler O, Ferenc A, *et al*. Physiologically low oxygen concentrations in fetal skin regulate hypoxia-inducible factor 1 and transforming growth factor-3. FASEB J. 2002;16(3):411-3. https://doi.org/10.1096/fj.01-0496fje
PMid:11790723

35. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol. 1927;8(6):519-30. https://doi.org/10.1085/jgp.8.6.519
PMid:19872213

36. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes
PMid:19620249

37. Chaturvedi P, Gilkes DM, Wong CC, Luo W, Zhang H, Wei H, *et al*. Hypoxia- inducible factor-dependent breast cancer-mesenchymal stem cell bidirectional signaling promotes metastasis. J Clin Invest. 2013;123(1):189-205. https://doi.org/10.1158/1538-7445.am2013-505
PMid:23318994

38. Yeung SJ, Pan J, Lee MH. Roles of p53, Myc and HIF-1 in regulating glycolysis: The seventh hallmark of cancer. Cell Mol Life Sci. 2008;65(24):3981-999. https://doi.org/10.1007/s00018-008-8224-x
PMid:18766298

39. Zhang H. HIF-1 suppresses lipid catabolism to promote cancer progression. Mol Cell Oncol. 2015;2(4):980184. https://doi.org/10.4161/23723556.2014.980184
PMid:27308514

40. Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP. Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors ininsulin resistance syndrome. Am J Epidemiol. 2000;152(10):897-907. https://doi.org/10.1093/aje/152.10.897
PMid:11092431

41. Jiang F, Tang YT, Guo L, Jiao XY. The role of insulin-like growth factor i and hypoxia inducible factor 1α in vascular endothelial growth factor expression in Type 2 diabetes. Ann Clin Lab Sci. 2013;43(1):37-44. https://doi.org/10.1161/hypertensionaha.115.06412
PMid:23462604

42. Xing F, Okuda H, Watabe M, Kobayashi A, Pai SK, Liu W, *et al*. Hypoxia induced Jagged2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells. Oncogene. 2011;30(39):4075-86. https://doi.org/10.1038/onc.2011.122
PMid:21499308