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Anemia is inversely associated with serum C-peptide concentrations in individuals with type 2 diabetes

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Abstract

The purpose of the study was to test the hypothesis that anemia is related with serum C-peptide concentrations in individuals with type 2 diabetes mellitus (DM).

This cross-sectional study was carried out in 1300 individuals with type 2 DM. We measured fasting C-peptide, 2-hour postprandial C-peptide, and postprandial C-peptide minus fasting C-peptide (ΔC-peptide) concentrations. Anemia was defined as hemoglobin (Hb) concentrations <130 g/L in men and <120 g/L in women. Anemia was graded into 2 groups: grade I anemia of Hb concentrations ≥110 g/L and grade II anemia of Hb concentrations <110 g/L.

Fasting C-peptide, postprandial C-peptide, and ΔC-peptide concentrations were lower in individuals with anemia. According to the grade of anemia, the average C-peptide concentrations differed significantly after adjusting for other covariates. In the multivariable model, the statistically significant relation between anemia and serum C-peptide concentrations remained after adjusting for confounders, including age, gender, family history of diabetes, body mass index, duration of diabetes, glycated Hb, free fatty acids, hypertension, and hyperlipidemia (fasting C-peptide concentration: β = –0.057, $P = .032$; postprandial C-peptide concentration: β = –0.098, $P < .001$; ΔC-peptide concentration: β = –0.095, $P < .001$).

Anemia was inversely associated with serum C-peptide concentrations in individuals with type 2 DM.

Abbreviations: DM = diabetes mellitus, Hb = hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation.

Keywords: anemia, C-peptide, fasting, postprandial period, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (DM) is characteristically progressive in nature.[1] The defects in pancreatic beta cell function contribute to the onset and the progression of type 2 DM. For these reasons, more rigorous interventions are needed to circumvent the loss of glycemic control over time.[1] However, the natural course of type 2 DM may vary in individual patients. Previous research has demonstrated that in individuals with type 2 DM, there are differences in the rates of reduction in beta cell function.[2] This heterogeneity of beta cell failure indicates that multiple factors might contribute to the progressive deterioration in beta cell function.

C-peptide is a molecule that connects the α-chain and the β-chain in proinsulin.[3] In the course of the cleavage from proinsulin, C-peptide is released with insulin in equimolar concentrations.[3] Due to its negligible hepatic degradation, peripheral C-peptide concentrations indicate portal insulin secretion more reliably than peripheral insulin concentrations.[4,5] In addition, its metabolic clearance rate is constant. Serum C-peptide concentration is therefore clinically useful as a surrogate marker of endogenous insulin secretion and for determination of diabetes regimens.[5,6]

Anemia is common in individuals with diabetes.[7] Anemia has detrimental effects on the ability to work, sense of well-being, and quality of life. Anemia contributes to an increased risk for cardiovascular events, dementia, and mortality.[8,9] In addition, previous studies have reported that anemia is implicated in diabetes-associated organ damage such as diabetic microangiopathy.[8,10] However, the information on the relationship between anemia and pancreatic beta cell function is limited in individuals with type 2 DM, although anemia results in tissue hypoxia.[8]

Therefore, we tested the hypothesis that anemia is associated with serum C-peptide concentrations in individuals with type 2 DM.

2. Methods

2.1. Participants

A total of 1300 individuals with type 2 DM who visited the diabetes clinic of Chonnam National University Hospital

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between January 2013 and December 2015 were randomly selected in this cross-sectional study. Type 2 DM was diagnosed on the basis of the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus."[11] The presence of hypertension was considered if the patient had blood pressure greater than 140/90 mm Hg or antihypertensive drugs were administered. Hyperlipidemia was defined as serum concentrations of total cholesterol ≥6.5 mmol/L and/or triglycerides ≥2.3 mmol/L, or a history of receiving lipid-lowering agents. Anemia was defined as hemoglobin (Hb) concentrations <130 g/L in men and <120 g/L in women.[12] Anemia was graded into 2 groups: grade I anemia of Hb concentrations ≥110 g/L and grade II anemia of Hb concentrations <110 g/L. The clinical data, including diabetes duration, smoking status, and other health-related variables, were obtained through standardized questionnaires. Individuals with a history of glucocorticoid treatment, positive antiglutamic acid decarboxylase antibodies, renal dysfunction (serum creatinine > 106 mmol/L), pancreatitis, chronic liver disease, infection, malignancy, alcoholism, hemolysis, blood loss, hemoglobinopathies, or blood transfusion were excluded from the study. Individuals requiring insulin treatment within 1 year of diagnosis were also excluded. The study was approved by an ethics committee of Chonnam National University Hospital. Informed consent was provided by all participants.

2.2. Measurement

Venous blood samples were obtained without the patients receiving oral antihyperglycemic agents or insulin between 8:00 h and 10:00 h after an overnight fast. For glycemic control, the antidiabetic drug courses were maintained until 1 day before performing the blood tests.

After collecting fasting blood samples, subjects received a standardized meal (10 kcal/kg; 60% carbohydrate, 20% protein, and 20% fat) according to the recommendations of the Korean Diabetes Association.[13] Blood samples were collected to measure the concentrations of glucose and C-peptide 2 hours after the meal. We calculated the change (Δ) in C-peptide concentrations as the postprandial serum C-peptide concentrations minus the fasting C-peptide concentrations. We measured Hb concentrations using cyanmethemoglobin spectrophotometry (Beckman-Coulter Inc., Miami, FL). We analyzed glycated Hb (A1C) by means of ion exchange liquid chromatography using the HLC-723-GHbV apparatus (Tosoh, Tokyo, Japan). We measured plasma glucose concentrations using the hexokinase method (Daiichi, Tokyo, Japan). We measured serum C-peptide concentrations using a radioimmunoassay (Biosource Europe SA, Nivelles, Belgium). The intra- and interassay coefficients of variation were 3.4% and 7.5%, respectively. Concentrations of triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were determined (AU5400; Olympus, Tokyo, Japan). Free fatty acid concentrations were analyzed by means of a colorimetric method using the NEFA-HR kit (Wako, Kyoto, Japan).

2.3. Statistical analyses

Data are provided as means ± standard deviations (SDs), unless otherwise described. The variables were tested for normal distribution using the Kolmogorov–Smirnov test. For the parameters with skewed distribution, log-transformation was implemented before performing the analysis and the data were represented as a geometric mean (95% confidence interval). For categorical variables, the Chi-square test was performed, while for continuous variables, the Mann–Whitney *U* test or Student *t* test was used. To compare mean C-peptide concentrations according to the grade of anemia, analysis of covariance was conducted after adjusting for confounding factors. The associations between anemia and serum C-peptide concentrations were analyzed using multiple linear regression models with identified factors and previously reported risk factors. Age, body mass index (BMI), duration of diabetes, A1C, and hypertension were included as covariates, because these parameters were significantly associated with C-peptide concentrations in the univariable analysis. Hyperlipidemia, free fatty acids, and familial diabetes were also considered as covariates, because these factors have previously been reported to be associated with beta cell function.[14,15] In addition, gender was included as a covariate. Highly intercorrelated ($r > 0.2$) variables were not entered in the same model. Because fasting and postprandial glucose levels were highly correlated with A1C levels, fasting and postprandial glucose concentrations were not included as the covariates. Statistical analyses were carried out using statistical package SPSS version 20.0 (SPSS, Chicago, IL). A *P* value of less than .05 indicated statistical significance.

3. Results

The characteristics of the individuals with type 2 DM are represented in Table 1. Individuals with anemia were older and had longer durations of diabetes; lower BMI; and lower concentrations of serum total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and free fatty acids than those without anemia. Individuals with anemia were associated with a higher prevalence of hypertension and a lower prevalence of hyperlipidemia than those without anemia. In addition, individuals with anemia had lower concentrations of fasting C-peptide, postprandial C-peptide, and ΔC-peptide than those without anemia.

The average values of serum C-peptide concentrations according to the grade of anemia are summarized in Table 2. After adjusting for age, gender, family history of diabetes, BMI, free fatty acids, A1C levels, diabetes duration, hypertension, and hyperlipidemia, serum C-peptide concentrations were found to be significantly different according to the grade of anemia (fasting C-peptide concentration: no anemia 0.73 mmol/L, grade I anemia 0.66 mmol/L, grade II anemia 0.62 mmol/L, *P* for trend = .002; postprandial C-peptide concentration: no anemia 1.54 mmol/L, grade I anemia 1.36 mmol/L, grade II anemia 1.32 mmol/L, *P* for trend < .001; ΔC-peptide concentration: no anemia 0.75 mmol/L, grade I anemia 0.64 mmol/L, grade II anemia 0.60 mmol/L, *P* for trend < .001, respectively).

Using linear regression models, we analyzed the relationship between the presence of anemia and serum C-peptide concentrations (Table 3). There was a significant association between the presence of anemia and serum C-peptide concentrations, with adjustments for variables including age, gender, family history of diabetes, BMI, free fatty acids, A1C levels, diabetes duration, hypertension, and hyperlipidemia (fasting C-peptide concentration: $\beta = -0.057$, $P = .032$; postprandial C-peptide concentration: $\beta = -0.098$, $P < .001$; ΔC-peptide concentration: $\beta = -0.095$, $P < .001$).

4. Discussion

In this study, we found a negative association between anemia and serum C-peptide concentrations in individuals with type 2

Table 1

Characteristics of subjects with type 2 diabetes according to the presence of anemia.

	Anemia (−)	Anemia (+)	P
n	735	565	
Age, y	56.8 ± 14.4	62.7 ± 13.7	< .001
Men (%)	392 (53.3)	255 (45.1)	.003
Diabetes duration, y	4.2 (3.8–4.6)	6.7 (6.1–7.4)	< .001
Body mass index, kg/m^2	25.1 ± 3.9	23.4 ± 4.4	< .001
Hypertension, n (%)	376 (51.2)	323 (57.2)	.031
Hyperlipidemia, n (%)	333 (45.3)	210 (37.2)	.003
Family history of diabetes, n (%)	245 (33.3)	190 (33.6)	.911
Smoking, n (%)	131 (17.8)	87 (15.4)	.246
Systolic blood pressure, mm Hg	124.3 ± 16.1	124.5 ± 16.7	.848
Diastolic blood pressure, mm Hg	76.3 ± 11.4	77.4 ± 10.5	.069
A1C, mmol/mol	73 ± 26	72 ± 28	.623
A1C (%)	8.8 ± 2.4	8.7 ± 2.6	.623
Fasting glucose, mmol/L	8.5 ± 3.4	8.3 ± 3.8	.554
Postprandial glucose, mmol/L	12.5 ± 4.8	12.6 ± 4.9	.790
Fasting C-peptide, mmol/L	0.74 (0.71–0.77)	0.64 (0.61–0.67)	< .001
Postprandial C-peptide, mmol/L	1.60 (1.52–1.67)	1.29 (1.22–1.36)	< .001
ΔC-peptide, mmol/L	0.79 (0.73–0.84)	0.60 (0.55–0.65)	< .001
Total cholesterol, mmol/L	4.7 ± 1.1	4.4 ± 1.5	< .001
Triglyceride, mmol/L	1.5 (1.5–1.6)	1.4 (1.3–1.4)	< .001
HDL-cholesterol, mmol/L	1.2 ± 0.3	1.1 ± 0.3	.001
LDL-cholesterol, mmol/L	2.9 ± 1.0	2.6 ± 1.0	< .001
Free fatty acid, nmoL/L	603.1 (524.1–705.6)	482.6 (425.9–560.5)	.003
Hemoglobin, g/L	139.9 ± 12.8	108.8 ± 11.7	< .001
Therapy, n (%)			.116
No medication	72 (9.8)	38 (6.7)	
OHA	449 (61.1)	338 (59.8)	
Insulin	126 (17.1)	106 (18.8)	
OHA + Insulin	88 (12.0)	83 (14.7)	

Data are represented as the mean ± standard deviation or geometric mean (95% CI). Numbers in parentheses indicate the percentage.
A1C = glycated hemoglobin, HDL-cholesterol = high-density lipoprotein cholesterol, LDL-cholesterol = low-density lipoprotein cholesterol, OHA = oral hypoglycemic agent.

DM. Because anemia causes hypoxic damages in the tissue, our data might support the hypothesis that anemia plays an important role in beta cell impairment in individuals with type 2 DM, even though the causative nature of its relationship could not be established in the current study.

In individuals with type 2 DM, anemia is frequently observed.[16] In diabetic individuals with or without diabetic nephropathy, Hb concentrations might diminish continually with time, as shown in previous studies.[7,16] Previous clinical studies have demonstrated that anemia increases cardiovascular morbidity and mortality.[17] Anemia elevates the risk of adverse cardiovascular consequences, including heart failure, ischemic heart disease, foot ulcers, and stroke.[8,18] Anemia might also result in diabetes-associated organ damage. Anemia has been reported to be implicated in an increased risk of diabetic retinopathy.[19,20] Reduced Hb concentrations aggravate diabetic kidney disease.[8] In addition, anemia is associated with diabetic neuropathy in individuals with type 2 DM.[8,21]

Accumulating evidence suggests that hypoxia might be involved in pancreatic beta cell damage, as beta cells are particularly susceptible to hypoxic stress.[22] Experimental data have suggested that beta cell hypoxia might be implicated in the progression of diabetes.[23–27] The disturbed vascular integrity of the islet is linked to beta cell failure in rodent models.[25] In the islets of animal models of type 2 DM, hypoxia-related genes are upregulated.[25,28] Recently, Sato et al[29] demonstrated that moderate hypoxia induces defects in insulin secretion in pancreatic beta cells. In addition, several clinical studies showed that obstructive sleep apnea causing intermittent hypoxia might be associated with an increased risk of disturbed glucose metabolism and type 2 DM.[30,31] However, in clinical practice, the association between anemia and beta cell function in individuals with type 2 DM has not been fully clarified.

In the present study, our data showed an inverse association between anemia and serum C-peptide concentrations in individuals with type 2 DM. Previous research has also shown that metabolic environments might be implicated in defective

Table 3

Multivariable linear regression analysis with serum C-peptide concentrations as a dependent variable.

	Partial regression coefficient (SE)	Standard partial regression coefficient	P
Fasting C-peptide level*			
Anemia (+)	−0.020 (0.009)	−0.057	.032
Body mass index	0.010 (0.001)	0.243	< .001
A1C	−0.018 (0.002)	−0.255	< .001
Diabetes duration*	−0.043 (0.010)	−0.113	< .001
R^2 (adjusted R^2)		0.218 (0.213)	
Postprandial C-peptide level*			
Anemia (+)	−0.047 (0.012)	−0.098	< .001
Body mass index	0.010 (0.001)	0.180	< .001
A1C	−0.040 (0.002)	−0.411	< .001
Diabetes duration*	−0.091 (0.013)	−0.173	< .001
R^2 (adjusted R^2)		0.312 (0.307)	
ΔC-peptide level*			
Anemia (+)	−0.055 (0.015)	−0.095	< .001
Body mass index	0.007 (0.002)	0.097	< .001
A1C	−0.046 (0.003)	−0.401	< .001
Diabetes duration*	−0.102 (0.017)	−0.162	< .001
R^2 (adjusted R^2)		0.236 (0.231)	

Adjusted for age, gender, family history of diabetes, free fatty acid*, hypertension, and hyperlipidemia.
A1C = glycated hemoglobin.
* Data were log-transformed before analysis.

Table 2

Comparison of means of C-peptide concentrations according to the grade of anemia.

Anemia grade	Fasting C-peptide, mmol/L Mean (95% CI)	Postprandial C-peptide, mmol/L Mean (95% CI)	ΔC-peptide, mmol/L Mean (95% CI)
No anemia	0.73 (0.70–0.77)	1.54 (1.47–1.60)	0.75 (0.71–0.80)
Grade I anemia	0.66 (0.61–0.71)	1.36 (1.27–1.45)	0.64 (0.58–0.71)
Grade II anemia	0.62 (0.56–0.68)	1.32 (1.23–1.42)	0.60 (0.53–0.67)
P for trend	.002	< .001	.001

Adjusted for age, gender, family history of diabetes, body mass index, free fatty acids, A1C levels, diabetes duration, hypertension, and hyperlipidemia.
A1C = glycated hemoglobin, CI = confidence interval.

insulin secretion in type 2 DM.[14] Glucose toxicity, lipotoxicity, and glucolipotoxicity have been suggested to play important roles in impaired beta cell function.[32,33] In chronic hyperglycemic environments, pancreatic beta cells might exhibit desensitization to glucose stimuli with reduced expression of the insulin gene, and prolonged exposure of excessive fatty acids might cause impaired conversion of proinsulin to insulin and defective insulin secretion.[1] BMI and diabetes duration have also been recognized to affect beta cell function.[34] Consistent with the findings of previous studies,[17,21] our results showed that anemia was related to diabetes duration, BMI, and dyslipidemia, which are linked to beta cell function.[14,34] Therefore, the association between anemia and serum C-peptide concentrations in the present study might be partially affected by these factors. However, in the multivariable analysis, the statistically significant relationships between anemia and serum C-peptide concentrations were persistent, after adjusting for confounders, including age, gender, family history of diabetes, BMI, free fatty acids, A1C levels, diabetes duration, hypertension, and hyperlipidemia. These findings therefore indicated that these factors did not have a significant impact on the association between anemia and C-peptide.

In our previous study that was conducted in 337 male patients with type 2 DM, we found an independent association between Hb concentrations and ΔC-peptide concentrations,[35] implying that Hb might be related to C-peptide concentrations. In the present study, we observed that the presence of anemia was inversely associated with the fasting C-peptide, postprandial C-peptide, and ΔC-peptide concentrations in the multivariable analysis, and these relations were independent of gender. Furthermore, these parameters of C-peptide measured in this study were related to the grade of anemia. Therefore, our data extend the previous findings, and suggest that, independently of gender, established or aggravated anemia might have detrimental effects on both fasting and postprandial C-peptide concentrations in individuals with type 2 DM.[36,37]

Even though the mechanism by which anemia contributes to pancreatic beta cell dysfunction is currently unclear, there are possible explanations. As there is high oxygen demand in pancreatic beta cells to generate adenosine triphosphate for insulin secretion, the availability of appropriate oxygen is pivotal for beta cells.[23,24,38] Thus, decreased oxygen delivery due to anemia might lead to the detrimental hypoxic state in beta cells. In addition, hypoxia could induce apoptosis,[29,39] which is observed in pancreatic beta cells in individuals with type 2 DM.[40] Hypoxia also inhibits adaptive unfolded protein response in pancreatic beta cells.[28] Lastly, anemia might result in increased oxidative stress,[41] which relates to a reduction in the absolute number of red blood cells with antioxidant defense and increased production of free radicals.[42,43] Increased oxidative stress might contribute to impaired beta cell function, because pancreatic beta cells exhibit low intrinsic antioxidant capacity and vulnerability to oxidative stress.[1]

Recent studies have demonstrated that beyond a marker for insulin secretory reserves, C-peptide might act as a biologically active molecule. C-peptide activates intracellular signaling pathways and it has beneficial effects on vascular endothelial function.[3] In individuals with type 1 DM, residual C-peptide concentrations are associated with the prevention of diabetic microvascular complications.[44] In addition, lower C-peptide concentrations might be linked to the increased risk of microangiopathy in individuals with type 2 DM.[45–47] In the current study, the negative relation between anemia and serum C-peptide concentrations might warrant investigating the association between C-peptide and microangiopathy in terms of anemia in individuals with type 2 DM.

This study has some limitations. First, this study is cross-sectional, and we therefore could not determine the causative nature of the relationships. Second, we did not address the cause of anemia in the present study. However, because anemia is considered as a reduction in Hb concentrations irrespective of its etiology,[12] it seems unlikely that it might have a significant impact on our findings. Finally, because the current research was performed in 1 center and the study population was limited to 1 ethnic group, our data might not be generalized to all individuals with type 2 DM.

In conclusion, the current study showed that the presence of anemia was inversely associated with serum C-peptide concentrations in individuals with type 2 DM. Further prospective investigations are required to establish the causal effects of anemia regarding the natural course of type 2 DM.

Author contributions

Conceptualization: Min Young Chung, Jin Ook Chung.
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References

[1] Robertson RP, Harmon J, Tran PO, et al. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes 2004;53(suppl 1):S119–24.
[2] Levy J, Atkinson AB, Bell PM, et al. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. Diabet Med 1998;15:290–6.
[3] Wahren J, Ekberg K, Johansson J, et al. Role of C-peptide in human physiology. Am J Physiol Endocrinol Metab 2000;278:E759–68.
[4] Field JB. Extraction of insulin by liver. Annu Rev Med 1973;24:309–14.
[5] Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013;30:803–17.
[6] Munshi MN, Hayes M, Sternthal A, et al. Use of serum c-peptide level to simplify diabetes treatment regimens in older adults. Am J Med 2009;122:395–7.
[7] Thomas MC, MacIsaac RJ, Tsalamandris C, et al. Unrecognized anemia in patients with diabetes: a cross-sectional survey. Diabetes Care 2003;26:1164–9.
[8] Thomas MC. Anemia in diabetes: marker or mediator of microvascular disease? Nat Clin Pract Nephrol 2007;3:20–30.
[9] Jeong SM, Shin DW, Lee JE, et al. Anemia is associated with incidence of dementia: a national health screening study in Korea involving 37,900 persons. Alzheimers Res Ther 2017;9:94.
[10] Singh DK, Winocour P, Farrington K. Erythropoietic stress and anemia in diabetes mellitus. Nat Rev Endocrinol 2009;5:204–10.
[11] Expert Committee on the Diagnosis and Classification of Diabetes MellitusReport of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26(suppl 1):S5–20.
[12] World Health OrganizationHaemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System World Health Organization, Geneva:2011;1–6.
[13] Ahn HJ, Han KA, Kwon HR, et al. Small rice bowl-based meal plan versus food exchange-based meal plan for weight, glucose and lipid control in obese type 2 diabetic patients. Korean Diabetes J 2010;34:86–94.

[14] Wajchenberg BL. beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev 2007;28:187–218.
[15] Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009;32(suppl 2):S151–6.
[16] Craig KJ, Williams JD, Riley SG, et al. Anemia and diabetes in the absence of nephropathy. Diabetes Care 2005;28:1118–23.
[17] Zoppini G, Targher G, Chonchol M, et al. Anaemia, independent of chronic kidney disease, predicts all-cause and cardiovascular mortality in type 2 diabetic patients. Atherosclerosis 2010;210:575–80.
[18] Barlas RS, Honney K, Loke YK, et al. Impact of hemoglobin levels and anemia on mortality in acute stroke: analysis of UK Regional Registry data, systematic review, and meta-analysis. J Am Heart Assoc 2016;5:
[19] Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. Invest Ophthalmol Vis Sci 1998;39:233–52.
[20] Qiao Q, Keinanen-Kiukaanniemi S, Laara E. The relationship between hemoglobin levels and diabetic retinopathy. J Clin Epidemiol 1997;50:153–8.
[21] Ito H, Takeuchi Y, Ishida H, et al. Mild anemia is frequent and associated with micro- and macroangiopathies in patients with type 2 diabetes mellitus. J Diabetes Investig 2010;1:273–8.
[22] Gerber PA, Rutter GA. The role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus. Antioxid Redox Signal 2017;26:501–18.
[23] Sato Y, Endo H, Okuyama H, et al. Cellular hypoxia of pancreatic beta-cells due to high levels of oxygen consumption for insulin secretion in vitro. J Biol Chem 2011;286:12524–32.
[24] Bensellam M, Duvillie B, Rybachuk G, et al. Glucose-induced O (2) consumption activates hypoxia inducible factors 1 and 2 in rat insulin-secreting pancreatic beta-cells. PLoS One 2012;7:e29807.
[25] Li X, Zhang L, Meshinchi S, et al. Islet microvasculature in islet hyperplasia and failure in a model of type 2 diabetes. Diabetes 2006;55:2965–73.
[26] Sato Y, Tsuyama T, Sato C, et al. Hypoxia reduces HNF4alpha/MODY1 protein expression in pancreatic beta-cells by activating AMP-activated protein kinase. J Biol Chem 2017;292:8716–28.
[27] Puri S, Cano DA, Hebrok M. A role for von Hippel-Lindau protein in pancreatic beta-cell function. Diabetes 2009;58:433–41.
[28] Bensellam M, Maxwell EL, Chan JY, et al. Hypoxia reduces ER-to-Golgi protein trafficking and increases cell death by inhibiting the adaptive unfolded protein response in mouse beta cells. Diabetologia 2016;59:1492–502.
[29] Sato Y, Inoue M, Yoshizawa T, et al. Moderate hypoxia induces beta-cell dysfunction with HIF-1-independent gene expression changes. PLoS One 2014;9:e114868.
[30] Botros N, Concato J, Mohsenin V, et al. Obstructive sleep apnea as a risk factor for type 2 diabetes. Am J Med 2009;122:1122–7.
[31] Priou P, Le Vaillant M, Meslier N, et al. Independent association between obstructive sleep apnea severity and glycated hemoglobin in adults without diabetes. Diabetes Care 2012;35:1902–6.
[32] Lupi R, Del Guerra S, Tellini C, et al. The biguanide compound metformin prevents desensitization of human pancreatic islets induced by high glucose. Eur J Pharmacol 1999;364:205–9.
[33] Lupi R, Del Guerra S, Marselli L, et al. Rosiglitazone prevents the impairment of human islet function induced by fatty acids: evidence for a role of PPARgamma2 in the modulation of insulin secretion. Am J Physiol Endocrinol Metab 2004;286:E560–7.
[34] Funakoshi S, Fujimoto S, Hamasaki A, et al. Analysis of factors influencing pancreatic beta-cell function in Japanese patients with type 2 diabetes: association with body mass index and duration of diabetic exposure. Diabetes Res Clin Pract 2008;82:353–8.
[35] Chung JO, Cho DH, Chung DJ, et al. Associations between hemoglobin concentrations and the clinical characteristics of patients with type 2 diabetes. Korean J Intern Med 2012;27:285–92.
[36] Kruszynska YT, Home PD, Hanning I, et al. Basal and 24-h C-peptide and insulin secretion rate in normal man. Diabetologia 1987;30:16–21.
[37] Pham MN, Kolb H, Battelino T, et al. Fasting and meal-stimulated residual beta cell function is positively associated with serum concentrations of proinflammatory cytokines and negatively associated with anti-inflammatory and regulatory cytokines in patients with longer term type 1 diabetes. Diabetologia 2013;56:1356–63.
[38] Dionne KE, Colton CK, Yarmush ML. Effect of hypoxia on insulin secretion by isolated rat and canine islets of Langerhans. Diabetes 1993;42:12–21.
[39] Brunelle JK, Chandel NS. Oxygen deprivation induced cell death: an update. Apoptosis 2002;7:475–82.
[40] Butler AE, Janson J, Bonner-Weir S, et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102–10.
[41] Grune T, Sommerburg O, Siems WG. Oxidative stress in anemia. Clin Nephrol 2000;53(1 suppl):S18–22.
[42] Siems WG, Sommerburg O, Grune T. Erythrocyte free radical and energy metabolism. Clin Nephrol 2000;53(1 suppl):S9–17.
[43] Deicher R, Horl WH. Anaemia as a risk factor for the progression of chronic kidney disease. Curr Opin Nephrol Hypertens 2003;12:139–43.
[44] Panero F, Novelli G, Zucco C, et al. Fasting plasma C-peptide and micro- and macrovascular complications in a large clinic-based cohort of type 1 diabetic patients. Diabetes Care 2009;32:301–5.
[45] Kim BY, Jung CH, Mok JO, et al. Association between serum C-peptide levels and chronic microvascular complications in Korean type 2 diabetic patients. Acta Diabetol 2012;49:9–15.
[46] Bo S, Gentile L, Castiglione A, et al. C-peptide and the risk for incident complications and mortality in type 2 diabetic patients: a retrospective cohort study after a 14-year follow-up. Eur J Endocrinol 2012;167:173–80.
[47] Chung JO, Cho DH, Chung DJ, et al. Relationship between serum C-peptide level and diabetic retinopathy according to estimated glomerular filtration rate in patients with type 2 diabetes. J Diabetes Complications 2015;29:350–5.