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Association between serum hydrogen sulfide concentrations and dysglycemia: a population-based study

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Abstract

Background and aim: Hydrogen sulfide (H_2S), a signaling gasotransmitter, is involved in carbohydrate metabolism. Here, we aimed to assess the potential association between serum H_2S and dysglycemia in the framework of a population-based study.

Methods: Adults men and women with completed data (*n* = 798), who participated in the Tehran Lipid and Glucose Study (2014–2017) were included in the study. Medians of fasting serum H_2S concentration were compared across the glycemic status of the participants, defined as type 2 diabetes mellitus (T2DM), isolated impaired fasting glucose (IIFG), isolated impaired glucose tolerance (IIGT), combined IFG-IGT, and normal glycemia [i.e., those with both normal fasting glucose (NFG) and normal glucose tolerance (NGT)]. Multinomial logistic regression was used to assess potential associations between serum H_2S and the defined glycemic status.

Results: Mean age of the participants was 45.1 ± 14.0 y, and 48.1% were men. Prevalence of T2DM, IIFG, IIGT, and combined IFG-IGT was 13.9, 9.1, 8.1, and 4.8% respectively. No significant difference was observed in serum H_2S concentrations between the groups. Lower serum H_2S (< 39.6 μmol/L) was associated with an increased chance of having IIGT (OR = 1.96, 95% CI = 1.15–3.34) in the adjusted model.

Conclusion: Reduced serum H_2S level may be associated with impaired glucose tolerance.

Keywords: Hydrogen sulfide, Type 2 diabetes, Impaired fasting glucose, Impaired glucose tolerance

Introduction

Hydrogen sulfide (H_2S) is a signaling gasotransmitter with cytoprotective properties that has several physiological functions in the cardiovascular, neuronal, gastrointestinal, respiratory, and reproductive systems [1]. Hydrogen sulfide regulates neurotransmission, vascular tone, angiogenesis, cellular redox homeostasis [2, 3]; has an essential role in regulating cell growth and differentiation, mitochondrial biogenesis, adipose tissue metabolism; and is involved in inflammatory pathways [1, 4].

Hydrogen sulfide is endogenously synthesized in tissues that are involved in carbohydrate metabolism, i.e., pancreatic β-cells, liver, adipose tissue, skeletal muscle, and hypothalamus, thus regulating local and systemic glucose metabolism [5, 6]. In the liver, H_2S regulates glucose uptake, glycogen storage, gluconeogenesis, and mitochondrial function [7–9]. The role of H_2S in regulating pancreatic β-cell apoptosis and insulin secretion has remained inconclusive, and its effects within the β-cells seem to depend on the stage and type of diabetes [5, 6, 10]. Both inhibitory and stimulatory H_2S effects on insulin-induced glucose uptake and a dual role in the

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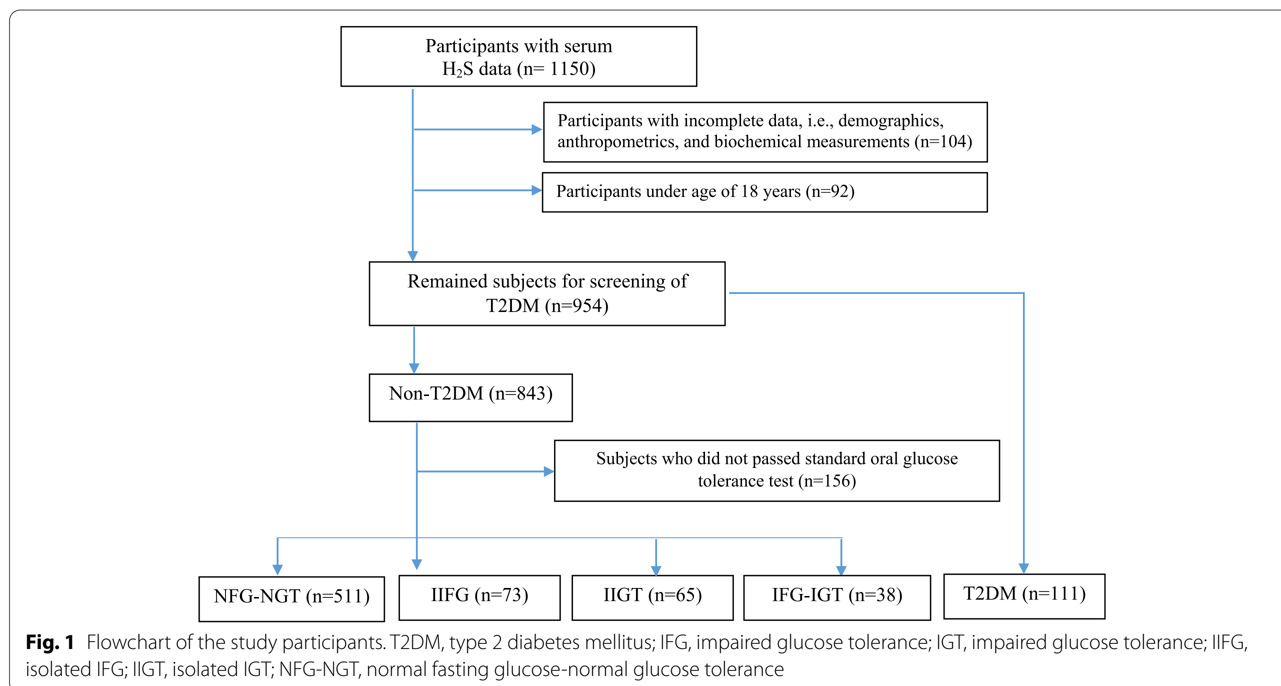

Fig. 1 Flowchart of the study participants. T2DM, type 2 diabetes mellitus; IFG, impaired glucose tolerance; IGT, impaired glucose tolerance; IIFG, isolated IFG; IIGT, isolated IGT; NFG-NGT, normal fasting glucose-normal glucose tolerance

development of insulin resistance have been illustrated [11–13].

Likewise, the potential role of H_2S in the pathophysiology of type 2 diabetes mellitus (T2DM) is controversial; endogenous H_2S synthesis has been reported to be decreased during obesity development, T2DM, and its complications [10, 14]. In addition, available evidence indicates that plasma H_2S levels are decreased in patients with T2DM [14, 15].

The aim of this study is to determine association between fasting serum H_2S levels and glycemic status in a population-based study.

Methods

Study population

This cross-sectional study was conducted among the participants of an ongoing community-based prospective study (the Tehran Lipid and Glucose Study, TLGS), which started in 1999 with 15,005 individuals, aged ≥ 3 years, to investigate and prevent non-communicable diseases [16]. For the current study, we recruited a sub-set of the participants comprising the sixth phase of the TLGS (2014–2017) to measure their serum H_2S concentrations ($n = 1150$). After exclusion of participants with incomplete data on demographics, anthropometrics, and biochemical measurements ($n = 104$) and those who were under age of 18 y ($n = 92$), 954 adult men and women remained for screening of T2DM subjects. Finally, subjects who did not passed standard oral glucose tolerance test (OGTT) were excluded ($n = 156$), and final analyses were conducted on 798 participants. The flowchart of the study participants is presented as Fig. 1.

Written informed consent was obtained from all participants. The ethics research council of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the study protocol (Ethics code: IR.SBMU.ENDOCRINE.REC.1400.074).

Demographic, anthropometric, and biochemical measurements

Details of data collection and measurements of the variables in the TLGS have been reported elsewhere [16]. In brief, anthropometric data, including body weight, height, and waist circumference (WC) were collected using standard methods. Body mass index (BMI) was calculated as weight (kg) divided by square of height in meters (m^2).

Systolic (SBP) and diastolic (DBP) blood pressures were measured using a standard mercury sphygmomanometer calibrated by the Institute of Standards and Industrial Research of Iran [17]. Blood pressure was measured twice on participants' right arm, after a 15-min rest in a sitting position, with at least a 30-s interval between two measurements. The mean of the two measurements was considered as the participant's blood pressure.

Details of biochemical measurements in the TLGS samples have been described elsewhere [18]. In brief, measurements of fasting serum glucose (FSG), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels were all done after a 12-to 14-h overnight fast. The standard oral glucose tolerance test (OGTT) was performed for all participants who were not on glucose-lowering medications.

Total serum sulfide levels were measured using the methylene blue method [19]. This is a spectrophotometric method based on methylene blue dye after the reaction of the sulfide and N, N-dimethyl-*p*-phenylenediamine [20]. In brief, serum (100 µL) was added to a test tube containing zinc acetate (1% *w*/*v*, 200 µL), *N*,*N*-dimethyl-*p*-phenylenediamine sulfate in 7.2 M HCl (20 mM, 100 µL), and $FeCl_3$ in 1.2 M HCl (30 mM, 133 µL). After incubation at 37 °C for 30 min, the tubes were centrifuged at 5000 g for 10 min. Supernatants were collected for the measurement of total sulfide. Total sulfide concentration was determined in the samples using a standard calibration curve (Supplementary Figure 1) established by 0–200 µM of sodium hydrosulfide (NaSH); optical density was read at wavelength of 670 nm using a microplate reader (BioTek, MQX2000R2, Winooski, VT, USA) [21]. Both intra- and inter-assay coefficients of variation (CV) were between 1.7–6.3%.

Definition of terms

Participants were categorized into different groups of glycemic status as follows [22, 23]: normal glycemia [i.e., normal fasting glucose (NFG) and normal glucose tolerance (NGT)], FSG < 100 and 2 hours serum glucose (2 h-SG) < 140; isolated impaired fasting glucose (IIFG), 100 ≤ FSG < 126 and 2 h-SG < 140 mg/dL; isolated impaired glucose tolerance (IIGT), 140 ≤ 2 h-SG < 200 and FSG < 100 mg/dL; combined IFG and IGT (IFG-IGT) was defined as having both 100 ≤ FSG < 126 and 140 ≤ 2 h-SG < 200 mg/dL; T2DM, FSG ≥ 126 mg/dL or 2 h-SG ≥ 200 mg/dL, or using glucose-lowering medications.

Statistical methods

Statistical analyses were conducted using the SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA) and the GraphPad Prism version 6.00 for Windows (GraphPad Software, CA, USA). Serum H_2S (due to a non-normal distribution, log-H_2S was included in the model) concentration were compared across the groups using analysis of covariance with adjustment of age and sex.

Association between serum H_2S and glycemic status was assessed using multinomial logistic regression analysis with subjects' glycemia status (NFG-NGT as reference, IIFG, IIGT, combined IFG-IGT, and T2DM) as the outcome variables and serum H_2S as the independent variable [either as continues ($\log_{10}$-H_2S) or categorical variable (< or ≥ median ≈39.6 µmol/L)]. Potential covariates were selected based on both statistical and scientific evidence. A univariate analysis was performed for potential confounding variables, and those with $P_E < 0.2$ were selected for the final multivariable model; P_E (*P*-value for entry) determines which variables should be included in the multivariable model [24]. Finally, two models, including crude and adjusted model (sex and subjects' age) were conducted.

Results

The mean age of the participants was 45.1 ± 14.0 y, and 48.1% were men. Prevalence of T2DM, IIFG, IIGT, and combined IFG-IGT was 13.9%, 9.1%, 8.1%, 4.8%, respectively. The characteristics of the study population, the anthropometric and biochemical measurements across glycemic conditions are summarized in Table 1. The median (inter-quartile range, IQR) of serum H_2S concentrations across the glycemic statuses of the participants are reported in Table 1. Result of analysis of covariance showed no significant difference in serum H_2S levels across the groups ($P = 0.533$).

The findings of multinomial logistic regression analyses are summarized in Table 2. Lower serum H_2S (< 39.6 µmol/L) was associated with an increased chance of having IIGT in the adjusted model (OR = 1.96, 95% CI = 1.15–3.34). No significant association was observed between serum H_2S and other dysglycemic conditions.

Discussion

To the best of our knowledge, this is the first population-based study investigating the potential association between glycemic status and total serum sulfide levels, a surrogate of the novel gasotransmitter H_2S, that is involved in glucose and insulin metabolism. Lower serum H_2S (< 39.6 µmol/L) was associated with an increased chance of having IIGT, however other dysglycemic conditions were not related to serum H_2S. This finding may imply that reduced H_2S may be involved in the pathogenesis of T2DM via insulin resistance and glucose intolerance pathways.

Few studies often limited by lacking enough statistical power are available concerning endogenous H_2S markers and glycemic parameters in humans. Median (IQR) plasma levels of H_2S were reported to be lower in T2DM patients compared to lean-aged matched and obese subjects [10.5 (4.8–22.0) µmol/L *vs.* 38.9 (29.7–45.1) and 22.0 (18.6–26.7) µmol/L, respectively] [15]. Likewise, a lower serum level of H_2S was detected in patients with T2DM compared with age-matched normal control subjects (110 *vs.* 130 µmol/L) [14]. Plasma H_2S levels were significantly lower in patients with T2DM compared to

Table 1 Characteristics of the study participants (*n* = 798)

	NFG-NGT (*n* = 511)	IIFG (*n* = 73)	IIGT (*n* = 65)	Combined IFG-IGT (*n* = 38)	T2DM (*n* = 111)
Age *(y)*	41.0 ± 12.6	47.1 ± 12.2	50.1 ± 14.1	55.8 ± 13.8	56.1 ± 12.5
Men *(%)*	46.6	50.7	47.7	50.0	53.2
FH *(%)*	7.4	12.5	7.8	10.8	16.2
BMI *(kg/m²)*	27.1 ± 5.0	30.4 ± 5.9	28.9 ± 4.9	29.8 ± 4.2	29.9 ± 4.8
WC *(cm)*	91.4 ± 11.7	99.3 ± 12.7	96.5 ± 10.8	100.0 ± 9.8	101.2 ± 11.2
SBP *(mm Hg)*	109 ± 13	118 ± 15	117 ± 18	121 ± 18	125 ± 17
DBP *(mm Hg)*	74 ± 9	79 ± 8	78 ± 11	75 ± 8	79 ± 8
FSG *(mg/dL)*	87.9 ± 6.5	104.4 ± 4.6	90.7 ± 5.1	107 ± 5.3	152.9 ± 59.5
2 h-SG *(mg/dL)*	98.9 ± 19.9	107.5 ± 18.5	156.4 ± 13.9	167.1 ± 15.7	243.7 ± 89.7[b]
TG *(mg/dL)*[a]	113 (80–159)	128 (98–194)	159 (123–204)	146 (120–213)	165 (118–224)
HDL-C *(mg/dL)*	48 ± 10	45 ± 11	44 ± 11	44 ± 11	43 ± 10
Serum H_2S *(μmol/L)* [a]	42.9 (22.2–81.0)	36.9 (17.4–88.1)	33.4 (19.3–70.9)	36.1 (9.3–81.1)	36.5 (18.9–71.1)

Data are mean ± SD (unless stated otherwise)

[a] Median (inter-quartile range)

[b] *n* = 32

T2DM type 2 diabetes mellitus, *FH* Family history of T2DM, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FSG* fasting serum glucose, *2 h-SG* 2-h serum glucose, *TG* serum triglyceride, *HDL-C* high-density lipoprotein cholesterol, *H_2S* hydrogen sulfide, *IFG* impaired glucose tolerance, *IGT* impaired glucose tolerance, *IIFG* isolated IFG, *IIGT* isolated IGT, *NFG-NGT* normal fasting glucose-normal glucose tolerance

Table 2 The odds ratio (95% CI) of having dysglycemia according to serum H_2S concentrations

	NGT-NFG	IIFG	IIGT	Combined IFG-IGT	T2DM
Log H_2S					
Crude	1.00	0.93 (0.54–1.58)	0.67 (0.39–1.13)	0.58 (0.31–1.11)	0.80 (0.52–1.24)
Adjusted model	1.00	0.95 (0.55–1.62)	0.70 (0.41–1.20)	0.64 (0.33–1.24)	0.88 (0.55–1.40)
H_2S (< median)					
Case/total (n)		38/73	41/65	21/38	60/111
Crude	1.00	1.24 (0.76–2.03)	1.96 (1.15–3.34)*	1.42 (0.73–2.75)	1.35 (0.89–2.04)
Adjusted model	1.00	1.27 (0.77–2.10)	1.97 (1.14–3.39)**	1.38 (0.69–2.74)	1.32 (0.84–2.06)

NGT-NFG was considered as the reference

Multinomial logistic regression was used (adjusted model included age and sex)

* *P* = 0.013, ** *P* = 0.014

Median serum H_2S was 39.6 μmol/*L*

T2DM type 2 diabetes mellitus, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *IIFG* isolated IFG, *IIGT* isolated IGT

healthy controls (45.1 ± 15.5 *vs.* 54.0 ± 26.4 μmol/L), and patients who had poor glycemic control had a more significant reduction in plasma H_2S levels [25]. Plasma H_2S levels were also negatively correlated with the glycosylated hemoglobin (HbA1c) level and disease duration [25].

Animal models of diabetes exhibited reduced serum H_2S concentrations without changes in the tissue expression of the H_2S synthesizing enzymes, cystathionine-β-synthase (CBS), and cystathionine-γ-lyase (CSE) [26]. These findings of in vivo studies suggest that hyperglycemia-induced H_2S reduction may be due to increased degradation in response to high-glucose concentrations [26]. Furthermore, reduced activity of H_2S-producing enzymes as seen in diabetes, reduces the production of endogenous H_2S and its circulatory levels [27]. Hydrogen sulfide deficiency has been suggested to be involved in the progression of diabetes and its complications [28].

In mammals, circulating H_2S concentrations have been reported to range from nanomolar to micromolar levels [29]. Physiological serum H_2S concentrations appear within a range of 30–300 μmol/L [30]. As with other gasotransmitters, i.e., nitric oxide (NO) and carbon monoxide (CO), biological effects of H_2S follow a biphasic dose–response, including physiological and

cytoprotective properties at low concentrations to cytotoxic effects at higher concentrations [31].

Our study has some limitations. Due to its cross-sectional design, it is difficult to make a causal inference between serum H_2S and dysglycemia, and the associations identified might be challenging to interpret. Another limitation was the method used to measure serum total sulfide level, the methylene blue method, which measures all sulfur species rather than only free-H_2S. Interference of other colored substances, formation of methylene blue dimer and trimer, strong acid chemical pretreatment, and low sensitivity have been documented as limitations of the method [20]. However, this method is commonly used for measuring H_2S in biological systems. As an strength, our findings may provide new insights into further investigations.

In conclusion, the findings of this cross-sectional study indicate that reduced serum H_2S concentrations may be associated with an impaired glucose tolerance. This may imply that H_2S deficiency is probably involved in or H_2S system is down-regulated during the progression of T2DM.

Abbreviations

2 h-SG: 2 hours serum glucose; BMI: Body mass index; DBP: Diastolic blood pressure; FSG: Fasting serum glucose; H_2S: Hydrogen sulfide; HDL-C: High-density lipoprotein cholesterol; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; IQR: Inter-quartile range; IIFG: Isolated impaired fasting glucose; IIGT: Isolated impaired glucose tolerance; NFG: Normal fasting glucose; NGT: Normal glucose tolerance; OGTT: Oral glucose tolerance test; OR: Odds ratio; SBP: Systolic blood pressure; SD: Standard deviation; T2DM: Type 2 diabetes mellitus; TG: Triglyceride; TLGS: Tehran Lipid and Glucose Study; WC: Waist circumference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-022-00995-8.

Additional file 1: Figure 1. Standard calibration curve of serum H_2S measurement.

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Authors' contributions

Z.B and A.Gh designed the study. Z.B, S.J and A.Gh analyzed the data. Z. B, A.Gh, P.M, and Kh.K wrote the manuscript. F.A supervised the work. All authors read and approved the final manuscript.

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Availability of data and materials

Data will be presented upon forwarding the request to the corresponding author (ghasemi@endocrine.ac.ir) and confirmation of the director of RIES (azizi@endocrine.ac.ir).

Declarations

Ethics approval and consent to participate

We obtained written informed consent from all participants. Based on the ethical guidelines of the 1975 Declaration of Helsinki, the study protocol was approved by the Ethics Research Council of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences.

Consent for publication

Not applicable.

Competing interests

The authors have no conflict of interest.

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References

1. Wallace JL, Wang R. Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. Nat Rev Drug Discov. 2015;14:329–45.
2. Kimura H. Physiological Roles of Hydrogen Sulfide and Polysulfides. Handb Exp Pharmacol. 2015;230:61–81.
3. Xie ZZ, Liu Y, Bian JS. Hydrogen Sulfide and Cellular Redox Homeostasis. Oxid Med Cell Longev. 2016;2016:6043038.
4. Wallace JL, Blackler RW, Chan MV, Da Silva GJ, Elsheikh W, Flannigan KL, Gamaniek I, Manko A, Wang L, Motta JP, Buret AG. Anti-inflammatory and cytoprotective actions of hydrogen sulfide: translation to therapeutics. Antioxid Redox Signal. 2015;22:398–410.
5. Zhang H, Huang Y, Chen S, Tang C, Wang G, Du J, Jin H. Hydrogen sulfide regulates insulin secretion and insulin resistance in diabetes mellitus, a new promising target for diabetes mellitus treatment? A review. J Adv Res. 2021;27:19–30.
6. Bahadoran Z, Mirmiran P, Ghasemi A. Hydrogen Sulfide and Carbohydrate Metabolism. In: Atta-ur-Rahman, editor. Frontiers in Clinical Drug Research (Diabetes and Obesity). Sharjah: Bentham Science Publishers. 2019;4:226–58.
7. Mani S, Cao W, Wu L, Wang R. Hydrogen sulfide and the liver. Nitric Oxide. 2014;41:62–71.
8. Zhang L, Yang G, Untereiner A, Ju Y, Wu L, Wang R. Hydrogen sulfide impairs glucose utilization and increases gluconeogenesis in hepatocytes. Endocrinology. 2013;154:114–26.
9. Guo W, Li D, You Y, Li W, Hu B, Zhang S, Miao L, Xian M, Zhu Y, Shen X. Cystathionine γ-lyase deficiency aggravates obesity-related insulin resistance via FoxO1-dependent hepatic gluconeogenesis. Faseb j. 2019;33:4212–24.
10. Gheibi S, Samsonov AP, Gheibi S, Vazquez AB, Kashfi K. Regulation of carbohydrate metabolism by nitric oxide and hydrogen sulfide: Implications in diabetes. Biochem Pharmacol. 2020;176:113819.
11. Manna P, Jain SK. Hydrogen sulfide and L-cysteine increase phosphatidylinositol 3,4,5-trisphosphate (PIP3) and glucose utilization by inhibiting phosphatase and tensin homolog (PTEN) protein and activating phosphoinositide 3-kinase (PI3K)/serine/threonine protein kinase (AKT)/

protein kinase Czeta/lambda (PKCzeta/lambda) in 3T3l1 adipocytes. J Biol Chem. 2011;286:39848–59.
12. Feng X, Chen Y, Zhao J, Tang C, Jiang Z, Geng B. Hydrogen sulfide from adipose tissue is a novel insulin resistance regulator. Biochem Biophys Res Commun. 2009;380:153–9.
13. Wijekoon EP, Hall B, Ratnam S, Brosnan ME, Zeisel SH, Brosnan JT. Homocysteine Metabolism in ZDF (Type 2) Diabetic Rats. Diabetes. 2005;54:3245–51.
14. Jain SK, Bull R, Rains JL, Bass PF, Levine SN, Reddy S, McVie R, Bocchini JA. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid Redox Signal. 2010;12:1333–7.
15. Whiteman M, Gooding KM, Whatmore JL, Ball CI, Mawson D, Skinner K, Tooke JE, Shore AC. Adiposity is a major determinant of plasma levels of the novel vasodilator hydrogen sulphide. Diabetologia. 2010;53:1722–6.
16. Azizi F, Zadeh-Vakili A, Takyar M. Review of Rationale, Design, and Initial Findings: Tehran Lipid and Glucose Study, Int J. Endocrinol Metab. 2018;16:e84777.
17. Askari S, Asghari G, Ghanbarian A, Khazan M, Alamdari S, Azizi F. Seasonal variations of blood pressure in adults: Tehran lipid and glucose study. Arch Iran Med. 2014;17:441–3.
18. Tohidi M, Ghasemi A, Hadaegh F, Derakhshan A, Chary A, Azizi F. Age- and sex-specific reference values for fasting serum insulin levels and insulin resistance/sensitivity indices in healthy Iranian adults: Tehran Lipid and Glucose Study. Clin Biochem. 2014;47:432–8.
19. Shen X, Pattillo CB, Pardue S, Bir SC, Wang R, Kevil CG. Measurement of plasma hydrogen sulfide in vivo and in vitro. Free Radic Biol Med. 2011;50:1021–31.
20. Shen X, Kolluru GK, Yuan S, Kevil CG. Measurement of H2S in vivo and in vitro by the monobromobimane method. Methods Enzymol. 2015;554:31–45.
21. Gheibi S, Jeddi S, Kashfi K, Ghasemi A. Effects of Hydrogen Sulfide on Carbohydrate Metabolism in Obese Type 2 Diabetic Rats. Molecules (Basel, Switzerland). 2019;24:190.
22. Genuth S, Alberti KG, Bennett P, Buse J, De Fronzo R, Kahn R, Kitzmiller J, KnowlerWC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up Report on the Diagnosis of Diabetes Mellitus. Diabetes Care. 2003;26:3160–7.
23. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B. Impaired Fasting Glucose and Impaired Glucose Tolerance Implications for care. Diabetes Care. 2007;30:753–9.
24. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley & Sons Inc; 2000.
25. Suzuki K, Sagara M, Aoki C, Tanaka S, Aso Y. Clinical Implication of Plasma Hydrogen Sulfide Levels in Japanese Patients with Type 2 Diabetes. Intern Med. 2017;56:17–21.
26. Suzuki K, Olah G, Modis K, Coletta C, Kulp G, Gero D, Szoleczky P, Chang T, Zhou Z, Wu L, Wang R, Papapetropoulos A, Szabo C. Hydrogen sulfide replacement therapy protects the vascular endothelium in hyperglycemia by preserving mitochondrial function. Proc Natl Acad Sci U S A. 2011;108:13829–34.
27. Peake BF, Nicholson CK, Lambert JP, Hood RL, Amin H, Amin S, Calvert JW. Hydrogen sulfide preconditions the db/db diabetic mouse heart against ischemia-reperfusion injury by activating Nrf2 signaling in an Erk-dependent manner. Am J Physiol Heart Circ Physiol. 2013;304:H1215–24.
28. Szabo C. Roles of hydrogen sulfide in the pathogenesis of diabetes mellitus and its complications. Antioxid Redox Signal. 2012;17:68–80.
29. Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev. 2012;92:791–896.
30. Olson KR. Is hydrogen sulfide a circulating "gasotransmitter" in vertebrate blood? Biochim Biophys Acta. 2009;1787:856–63.
31. Szabo C. Gaseotransmitters: new frontiers for translational science. Sci Transl Med. 2010;2:59ps54.

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