Diabetic acute ischaemic stroke patients have an increase in glycemic variations assessed by continuous glucose monitoring: a multi-center, observational study

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Research

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Abstract

Background One-third of acute ischaemic stroke (AIS) occurs in patients with an abnormal glucose metabolism, but little is known the differences in glycemic variations (GV) between stroke patients with and without abnormal glucose metabolism. The objective of this study was to observe the differences in GV between AIS patients with T2D and without T2D using continuous glucose monitoring (CGM).

Methods This was a multi-center, prospective, observational study performed between March 2018 and September 2018 in 5 hospitals in China. After admission, all recruited patients were subjected to a consecutive 4-day CGM. At the endpoint, patients were divided into two groups according to the T2D status. The primary outcome was the differences in GV between AIS patients with and without T2D.

Results A total of 149 patients (63 patients with T2D and 86 patients without T2D) were recruited into this study. AIS patients with T2D had a significant increase in the standard deviation of mean glucose, the mean amplitude glycemic excursions, the mean lowest glucose, the incremental area over the curve of hypoglycemia, the percentage of time spent in hypoglycemia, and the time in target range compared to those AIS patients without T2D ($p<0.05$ for all).

Conclusions Our data demonstrates that AIS patients with T2D had a significant increase in GV compared to those without T2D. Our results indicated that therapies aimed to improvement in GV may be important to a better clinical outcome in patients with AIS after the onset of a stroke.

Background

One-third of acute ischaemic stroke (AIS) occur in patients with abnormal glucose metabolism, and the two disorders often parallel. Controlled for demographic and other confounder risk factors, diabetes independently contributed to more than two-fold increase in ischaemic stroke and worsens the outcomes in patients with acute stoke [1–4]. Using continuous glucose monitoring (CGM) researchers documenting that AIS patients with a duration of persist hyperglycemia for at least 88 hours. However, a transient glucose decline was also observed[5], highlighting the fact that poststroke patients may experience a dynamic glucose change and a higher frequency of glucose monitoring is necessary for the identification of glycemic variations (GV)[5].

Studies based on single-point glucose level focused on the detrimental effects of hyperglycemia on stroke outcomes revealed that indicates that the admission blood glucose (ABG) was a potential predictor of poor outcome and increased mortality of AIS [6,7]. Study also observed that AIS patients with diabetes mellitus, especially with higher glycosylated haemoglobin levels were at a significantly increased risk for detrimental outcome compared to those with normal glucose metabolism[8]. Which indicates that increased glycemic variations in diabetic AIS patients may have a worsen clinical outcome in patients with AIS.

However, little is known the differences in glycemic variations (GV) between stroke patients with and without abnormal glucose metabolism. CGM provide glucose concentrations every 5 min for at least 72 hours, a set of metrics using data collected from CGM were employed presenting as GV, e,g. the standard deviation (SD), Coefficient of Variance (CV), the mean amplitude glycemic excursions (MAGE), the incremental area under curve (AUC) of hyperglycemia (> 10.0 mmol/L) and the incremental of area over curve (AOC) of hypoglycemia (< 3.9 mmol/L), and percentage of time in range (TIR) (3.9–10.0 mmol/L), and time spent in hyperglycemia.

We therefore performed a multi-center, prospective, observational study. In this study, we compared the differences in 24 hrs glycemic variations using CGM in AIS patient with and without T2D.

Methods

This was a multi-center, prospective, observational study performed at Department of Neurology, Yancheng No. 1 People's Hospital, the Fourth Affiliated Hospital of Nantong University, China; Department of Neurology, Taizhou People's Hospital; Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, China; Department of Neurology, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, China; and Department of Neurology, people's Hospital of Dezhou, China between March 2018 and September 2018. The inclusion criteria were 1) Inpatient with acute ischemic stroke (AIS) less than 6 hrs after AIS onset; 2) Patients aged between 18 and 80 years; 3) Patients with or without established T2D history. Patients were excluded if they had 1) hemorrhagic stroke or other etiologic type of stroke; and 2) type 1 diabetes. The study was approved by the ethics committee of Yancheng City No. 1 People's Hospital, the Fourth Affiliated Hospital of Nantong University, China and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, including any relevant details. Written informed consent was obtained from each research center.

On day 0 of admission, the patient's demographic data were collected by specially trained nurses. Modified Rankin scale (mRS) was assessed by a physician[9]. In addition, diabetic status, such as admission venous plasma glucose levels, the duration of diabetes, and patients receiving glucose-lowering agents, et al. were also recorded. On day 1 of admission, fasting serum samples were collected for HbA_{1c}, glucose, and C-peptide concentrations determination. HbA_{1c} was measured by a DiaSTAT HbA_{1c} analyzer (Bio-Rad, Hercules, CA). C-peptide and glucose levels were analyzed at each research center. All recruited patients were subjected a retrospective CGM (Sof-sensor, CGMS-Gold, Medtronic Incorporated, Northridge, USA) from day 0 of admission to day 4 of admission for consecutive 4-day, as described previously[10,11]. The CGM sensor was subcutaneously embedded and continually wear the sensor until the sensor functional expired. Four additional capillary finger-pricks for glucose measurements per day were made, with one measurement taken in the interval of no more than 8 hrs, for calibration purposes during CGM period. After 4 days of CGM, subjects had the sensors removed, the CGM data were collected and analyzed by the investigators, as described previously[10 – 12]. During the

CGM period, all subjects were instructed to maintain moderate physical activity and three meals per day consisting of a total daily caloric intake of 25 kcal/kg/day were served at 0700, 1100 and 1700 by research nurses, respectively, if patients were not in coma. Patients in a coma received Fatemulsion, Aminoacids (17) glucose (11) Injection infusions (Kabiveil PI, Sino-Swed Pharmaceutical Corp. Ltd, Wuxi, China) containing macronutrient, dextrose, and short-acting insulin, which was administered at a rate of 110 mL/h as previously prescribed[13]. Hypoglycemia, glucose level less than 3.9 mmol/L, was treated using IV glucose.

The 24-hr mean glucose (MG), the SDMG, the MAGE, the CV%, the mean highest glucose (MHG), the mean lowest glucose (MLG), the incremental AUC of hyperglycemia (> 10.0 mmol/L) and the incremental AOC of hypoglycemia (< 3.9 mmol/L), the percentage of time spent in hyperglycemia and hypoglycemia, the TIR, and glucose readings were analyzed, as previously described[14]. In addition, the times of hypoglycemia in each patient were also recorded.

To observe the differences in GV between diabetic AIS patients with or without parental nutrition (PN) therapy, a stratified analysis was performed comparing the MG, the SDMG, the MAGE, the CV%, the MHG, the MLG, the incremental AUC of hyperglycemia and the incremental AOC of hypoglycemia, the percentage of time spent in hyperglycemia and hypoglycemia and the TIR between the two groups.

The primary outcome was the differences in MAGE between AIS patients with and without T2D. Secondary endpoints were the differences in SD, CV%, MG, MHG, MLG, the incremental AUC of hyperglycemia and the incremental AOC of hypoglycemia, the percentage of time spent in hyperglycemia and hypoglycemia and the TIR in the two groups. In addition, the differences in GV in AIS patients with T2D receiving or not receiving PN were also compared.

Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL). All data were presented as the mean ± SD. Shapiro-Wilk test was used to verify the distribution of data. A Chi-squared test was performed compare the ratio differences between two groups. The mixed ANOVA model (2 × 2) test was used to compare differences between groups. All repeated data were analyzed by a two-way ANOVA between groups, followed by Bonferroni-Dunn post hoc test. P values were two-tailed with a significance level of 5%.

Results

Demographic characteristics of the enrolled subjects

A total of 160 stroke patients were screened for eligibility between March 2018 and September 2018. Eleven patients were excluded: 5 with capillary glucose concentrations above 22.2 mmol/L, 3 patients who did not meet the inclusion criteria, and another 3 patients had discontinuous CGM data. The data of 149 patients (63 patients with T2D and 86 patients without T2D), who finished the study and had CGM

data missing less than 10% were analyzed at the endpoint. Of the 149 enrolled patients, 113 (75.8%) had functional independence (mRS 0–2), and 36 (24.2%) had no or minimal disability (mRS 0–1).

The demographic characteristics of the enrolled subjects were described in detail between the two groups (Table 1). There were no differences in age, body weight, height, body mass index (BMI), admission blood glucose, and fasting blood glucose between AIS patients with or without T2D ($p > 0.05$ for all parameters). As expected, patients in T2D group had significant increase in HbA_{1c} levels ($p < 0.01$) and decrease in C peptide level ($p < 0.05$).

Table 1
Demographic characteristics in subjects between the groups at baseline

	AIS Group (n = 86)	AIS + Diabetes Group (n = 63)	p value
Sex (male)	71.0%	69.3%	0.88
Age (years)	66.4 ± 10.6	63.8 ± 11.3	0.36
Body weight (Kg)	65.2 ± 7.3	63.2 ± 7.4	0.76
Height (cm)	165.7 ± 5.7	163.9 ± 5.6	0.65
BMI (kg/m^2)	24.5 ± 3.6	23.8 ± 2.6	0.84
Course (years)	-	5.2 ± 3.6	0.00
HbA_{1c} (%)	5.7 ± 2.4	8.7 ± 2.1	0.00
ABG (mmol/L)	8.9 ± 2.7	9.8 ± 3.8	0.31
F C-peptide (ng/mL)	3.7 ± 1.2	1.5 ± 0.8	0.02

Data were presented as mean ± SD. BMI: Body mass index, Course: Course of diabetes, FBG: Fasting blood Glucose level, F C-peptide: Fasting C-Peptide concentration.

Glucose-lowering agent Profiles

All recruited subjects received glucose-lowering agents or/and combined with subcutaneous insulin administration in accordance with current stroke glucose management guidelines if they had glucose levels delivered by capillary above 10 mmol/L [15,16]. The diabetic duration in AIS patients with T2D was 5.2±3.6 years. All diabetic patients received glucose-lowering agents, with 5 patients (7.9%) receiving metformin alone therapy, 36 patients with insulin therapy (57.1%), 12 patients (19.0%) receiving metformin combination with insulin therapy, and 10 patients (15.9%) with other glucose-lowering agents. In addition, 24 patients (27.9%) without diabetic history received insulin therapy at least 20 units per day.

CGM profiles

Because CGM has a six hrs infiltration phage at the beginning of monitoring period and a sensor expire phage at the end of monitoring period, the measurements delivered from the two periods might not be reliable according to the manufacture's instruction. We therefore analyzed CGM data from the day 1 to day 3, and the day 0 and day 4 CGM date were not used in this study. In detail, all patients subjected CGM at 6–10 hrs after stroke onset and lasting for a median of 72 hrs, yielding 746±80 glucose readings per patient.

Our CGM data showed that there were no differences in the MG, the MHG, the incremental AUC of hyperglycemia, and the percentage of time spent in hyperglycemia between the two groups ($p>0.05$ for all). However, AIS patients with T2D had significant increase in the SDMG, the MAGE, the MLG, the incremental AOC of hypoglycemia, the percentage of time spent in hypoglycemia, and the TIR compared to those AIS patients without T2D ($p<0.05$ for all) (Table 2).

	AIS Group (n=86)	AIS +Diabetes Group (n=63)	P value
MG	8.6±3.7	9.5±1.6	0.07
SDMG	2.2±1.1	4.3±1.2	0.03
MAGE	4.5±2.8	6.4±3.5	0.01
MHG	10.2±1.9	15.5±3.1	0.02
MLG	5.6±1.7	5.2±1.4	0.88
CV	22.0±11.8	25.3±21.1	0.72
AUC>10	0.8±0.7	0.9±0.9	0.88
AOC<3.9	0.0±0.0	0.1±0.0	0.04
TIR	66.3±20.0	61.4±24.1	0.03
>10%	33.0±21.2	37.9±23.9	0.66
<3.9%	0.0±0.8	0.9±1.0	0.03

Data were presented as means ± SD. MG: mean glucose concentration (mmol/L), SDMG: standard deviation of MG (mmol/L), MAGE: mean amplitude of glycemic excursions (mmol/L), MHG: the mean highest glucose (mmol/L), MLG: the mean lowest glucose (mmol/L), CV: coefficient of variation (%), AUC>10: the incremental area under curve of glucose concentrations above 10 mmol/L (mmol/L per day), AOC<3.9: the incremental area over curve of glucose concentrations less than 3.9 mmol/L (mmol/L per day), TIR: time in the target range (%), >10%: time spent in hyperglycemia (>10 mmol/L) (%), <3.9%: time spent in hypoglycemia (<3.9 mmol/L) (%).

Table 2. Glycemic profiles between the groups in study subjects at the endpoint

No hypoglycemic episode was observed in AIS patients without T2D. However, our CGM data demonstrated that 9 patients (14%) experienced hypoglycemia episode (defined as glucose reading <3.9 mmol/L), with 4 patients experienced glucose levels less than 2.8 mmol/L, with severe hypoglycemia duration ranging from 15 min to 80 min. We therefore analyzed the times and duration of hypoglycemia in patients who had increase in incidences of hypoglycemia. We observed a total 105 times of hypoglycemia, and the total hypoglycemic duration was 220 min during the 3-day analyzed CGM period among all the recruited AIS patients.

Study reporting that male diabetic patients had an increased incidence of hypoglycemia during glucose-lowering therapy[14], so we therefore generated a stratified analysis comparing the incidence of hypoglycemia among male and female patients. Our data showed that male patients exhibited significant increase in hypoglycemic ratio compared to female patients (18% vs. 12%, $p<0.05$). In addition, we observed an increase in severe hypoglycemia (glucose <2.8 mmol/L) incidences in male patients compared to female patients (7.1% vs. 0, $p<0.01$). No differences in hypoglycemia times or hypoglycemia duration were observed between male and female groups ($p>0.05$, respectively).

To address the reliability of the blood glucose concentrations monitored by CGM in our study, we calculated the Mean Absolute Relative Difference (MARD) using software provided by Medtronic Incorporated, USA, which was the commonly used parameter to assess the reliability of CGM glucose readings according to instructions of Medtronic Incorporated, USA (if the venous blood glucose less than 5.6 mmol/L, the MARD should <18%, and if the venous blood glucose above 5.6 mmol/L, the MARD should <28%). In this study, the mean MARD was 10.5±4.1%, which confirms that our data collected from CGM using in this study was reliable.

It is known that patients receiving PN had a significantly higher incidence of malnutrition, in particular, hyperglycemia[17]. To support that notion, we next analyzed and compared the differences in the glycemic profiles between AIS patients with T2D receiving or not receiving PN (20 vs. 43). Although the patients had similar mean glucose levels between the two groups. We observed that patients in PN group had significant increases in the SDMG, the MAGE, the CV%, the MHG, the MLG, the incremental AUC of hyperglycemia, the incremental AOC of hypoglycemia, the percentage of time spent in hyperglycemia, the percentage of time spent in hypoglycemia, and the TIR ($p<0.05$ for all) (Table 3).

	With PN (n=20)	Without PN (n=43)	P value
MG	8.4±3.2	9.1±2.0	0.18
SDMG	5.1±3.4	2.2±3.0	0.04
MAGE	6.8±5.7	4.1±5.0	0.02
MHG	16.1±10.3	10.6±9.7	0.02
MLG	4.0±4.7	5.6±3.3	0.04
CV	33.4±19.6	23.8±20.2	0.02
AUC>10	0.9±0.2	0.7±0.5	0.04
AOC<3.9	0.1±0.0	0.0±0.0	0.04
TIR	45.7±42.3	60.3±29.2	0.03
>10%	39.2±28.4	30.7±20.6	0.04
<3.9%	0.8±0.8	0.2±1.0	0.03

Data were presented as means ± SD. PN: parental nutrition, MG: mean glucose concentration (mmol/L), SDMG: standard deviation of MG (mmol/L), MAGE: mean amplitude of glycemic excursions (mmol/L), MHG: the mean highest glucose (mmol/L), MLG: the mean lowest glucose (mmol/L), CV: coefficient of variation (%), AUC>10: the incremental area under curve of glucose concentrations above 10 mmol/L (mmol/L per day), AOC<3.9: the incremental area over curve of glucose concentrations less than 3.9 mmol/L (mmol/L per day), TIR: time in the target range (%), >10%: time spent in hyperglycemia (>10 mmol/L) (%), <3.9%: time spent in hypoglycemia (<3.9 mmol/L) (%).

Table 3. Glycemic profiles between the groups in diabetic AIS patients receiving or not PN at the endpoint

Safety And Tolerance

No episodes of patient-reported hypoglycemia requiring medical assistance were reported and all subjects were well tolerance with CGM during the study.

Discussion

This study revealed a novel observation that stroke patients with T2D had a significantly increased glycemic variations with regarding MAGE, SD, and CV% compared to those not having T2D. Patients receiving PN therapy may partially contribute to the increased GV. We further observed a significant

increase in severe hypoglycemia incidences in male patients when compared to female patients. Our data indicated that stroke patients with T2D should receive glucose-lowering therapies aimed at reducing the larger glycemic variations and the increased ratio of hypoglycemia.

A single measurement of glucose at admission or serial measurements after stroke onset may not necessarily reflect daily glycemic profiles during an AIS. CGM may be an optional tool describing the whole 24-hr glycemic profile. Metrics derived from CGM were already employed to assess the GV in diabetic patients[18 – 20]. However, little is known about the GV profiles in stroke patients with regarding the amplitude, the times and the duration of glucose ascending and descending after stroke onset. A previous study using CGM indicated that most stroke patients with or without impaired glucose metabolism experienced an ascending, a plateau, and a decreasing period in glucose levels lasting at least 72 hrs after stroke[5]. In accordance with the previous study, our data showed that the 3-day mean glucose concentrations monitored by CGM in patients with T2D were 9.5 ± 1.6 mmol/L, with the HMG more than 15 mmol/L, regardless whether or not the patients receiving multiple glucose-lowering therapies, which indicated patients enrolled into the pilot study were in the category of uncontrolled glucose were classified according to the guidelines set by European and U.S. stroke associations for the management of PSH[15,16]. In addition, we observed that stroke patients with T2D exhibited dramatically increased in glucose ascending and descending excursions. Studies focused on pathophysiological mechanisms demonstrated that acute glycemic variations, other than chronic hyperglycemia, exert a potential detrimental effectiveness on microvascular and macrovascular complications, via oxidative stress [21], suppression of NO production[22,23], inhibition of the fibrinolytic process[24], and an increase in coagulation[25 – 27]. Our results indicated that clinical researchers and clinicians should pay close attention to abate acute blood glucose fluctuations in glycemic management during post stroke, which might be important for an increased possibility of having an improvement of functional outcomes. Studies focused on the relationships between the alleviated acute GV and the improved functional recovery or independence are warranted.

Achieving euglycemic control in the early phage of stroke is difficult, the concerning for hypoglycemia may be an important barrier for patients with diabetes to achieve better glucose control[2]. One fourth of the patients receiving intensive insulin therapy experienced symptomless nocturnal hypoglycemia [28]. Studies further revealed that older diabetic patients had an significantly increased ratio of hypoglycemia compared to those of younger subjects [29,30]. In this study, the recruited patients were at mean 66 years age, we previously reported that older male diabetic patients (> 60 years old) had an increased potential incidence of nocturnal hypoglycemia. We expected that older male patients had a higher incidence of hypoglycemia compared to those of female patients. In this study, a total of 9 out 63 patients had hypoglycemia during the CGM period. A stratified analysis showed that men and women had similar incidence of hypoglycemia. However, our data indicating that male patients may exhibit a higher ratio of severe hypoglycemia, despite the fact that they received non-insulin glucose-lowering therapies. In this study, men and women had the similar age, course of disease, BMI, waistline, waist-to-hip ratio, and HbA1c values. It is unknown why the male patients had a higher incidence of severe hypoglycemia after a

stroke while receiving glucose-lowering therapy. However, this highlights that more frequency of blood glucose monitoring may be an optional way to prevent the incidence of hypoglycemia.

We also observed that AIS patients receiving PN had a significant increase in GV compared to those not receiving PN therapy. The significantly increased hyperglycemia and hypoglycemia during PN period may contribute to the increased GV in AIS patients receiving PN. Our results were in accordance with a previous study reporting that T2D patients receiving insulin required more different patterns of insulin doses during the PN period to maintain glycemic control, which may partially be the reason that the absorption and release of insulin from PN bag has some variations[31].

Our study has several limitations. Firstly, the study only observed patients from Jiangsu province in China, so the situation might not be the same for other populations. Secondly, the recruited subjects receiving various glucose-lowering therapies during the study period did not all respond in a similar manner. Thirdly, this was an observational study for a short period.

Conclusions

In conclusion, our data demonstrates that AIS patients with T2D had significant increase in GV, especially when PN therapy was needed. Our results indicated that more glucose measurements may be necessary to prevent hyperglycemia and hypoglycemia after a stroke onset may be beneficial.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Yancheng No. 1 People's Hospital, The Fourth Affiliated Hospital of Nantong University, China. All patients gave written informed consent. The methods were conducted in accordance with the Declaration of Helsinki guidelines, including any relevant details.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

No competing financial interests exist.

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Authors' contributions

H.R.X., and ZG. W. contributed to the conception and design of the study. FF. L., and G. L., contributed to the Conduct/data collection. XQ. G. contributed to data analysis. XN. G. contributed to manuscript writing. HR. X., and XN. G. final approval of the manuscript.

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References

1. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* Jun 26 2010;375(9733):2215-2222.
2. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke.* Jan 2001;32(1):280-299.
3. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. *The Lancet. Neurology.* Mar 2012;11(3):261-271.
4. Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Kappelle LJ, Dippel DW. Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. *Stroke.* Jun 2006;37(6):1413-1417.
5. Allport L, Baird T, Butcher K, et al. Frequency and temporal profile of poststroke hyperglycemia using continuous glucose monitoring. *Diabetes care.* Aug 2006;29(8):1839-1844.
6. Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology.* Sep 10 2002;59(5):669-674.
7. Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology.* Jul 9 2002;59(1):67-71.
8. Lattanzi S, Bartolini M, Provinciali L, Silvestrini M. Glycosylated Hemoglobin and Functional Outcome after Acute Ischemic Stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* Jul 2016;25(7):1786-1791.
9. Bruno A, Close B, Switzer JA, et al. Simplified modified Rankin Scale questionnaire correlates with stroke severity. *Clinical rehabilitation.* Aug 2013;27(8):724-727.
10. Li FF, Xu XH, Fu LY, et al. Influence of Acarbose on Plasma Glucose Fluctuations in Insulin-Treated Patients with Type 2 Diabetes: A Pilot Study. *International journal of endocrinology.* 2015;2015:903524.

11. Li FF, Fu LY, Zhang WL, et al. Blood Glucose Fluctuations in Type 2 Diabetes Patients Treated with Multiple Daily Injections. *Journal of diabetes research.* 2016;2016:1028945.
12. Zhou J, Li H, Ran X, et al. Reference values for continuous glucose monitoring in Chinese subjects. *Diabetes care.* Jul 2009;32(7):1188-1193.
13. Valero MA, Leon-Sanz M, Escobar I, Gomis P, de la Camara A, Moreno JM. Evaluation of nonglucose carbohydrates in parenteral nutrition for diabetic patients. *Eur J Clin Nutr.* Dec 2001;55(12):1111-1116.
14. Li FF, Zhang Y, Zhang WL, et al. Male Patients with Longstanding Type 2 Diabetes Have a Higher Incidence of Hypoglycemia Compared with Female Patients. *Diabetes therapy : research, treatment and education of diabetes and related disorders.* Oct 2018;9(5):1969-1977.
15. Olsen TS, Langhorne P, Diener HC, et al. European Stroke Initiative Recommendations for Stroke Management-update 2003. *Cerebrovasc Dis.* 2003;16(4):311-337.
16. Adams HP, Jr., Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke.* Apr 2003;34(4):1056-1083.
17. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* Jan-Feb 2002;26(1 Suppl):1SA-138SA.
18. Fabris C, Facchinetti A, Sparacino G, et al. Glucose variability indices in type 1 diabetes: parsimonious set of indices revealed by sparse principal component analysis. *Diabetes technology & therapeutics.* Oct 2014;16(10):644-652.
19. Fabris C, Facchinetti A, Fico G, Sambo F, Arredondo MT, Cobelli C. Parsimonious Description of Glucose Variability in Type 2 Diabetes by Sparse Principal Component Analysis. *Journal of diabetes science and technology.* Jul 31 2015;10(1):119-124.
20. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. *Diabetes technology & therapeutics.* Sep 2009;11(9):551-565.
21. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Jama.* Apr 12 2006;295(14):1681-1687.
22. Ding Y, Vaziri ND, Coulson R, Kamanna VS, Roh DD. Effects of simulated hyperglycemia, insulin, and glucagon on endothelial nitric oxide synthase expression. *American journal of physiology. Endocrinology and metabolism.* Jul 2000;279(1):E11-17.
23. Du XL, Edelstein D, Dimmeler S, Ju Q, Sui C, Brownlee M. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *The Journal of clinical investigation.* Nov 2001;108(9):1341-1348.
24. Ribo M, Molina C, Montaner J, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke.* Aug 2005;36(8):1705-1709.
25. Festa A, D'Agostino R, Jr., Mykkanen L, et al. Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance. The Insulin

Resistance Atherosclerosis Study (IRAS). *Arteriosclerosis, thrombosis, and vascular biology.* Mar 1999;19(3):562-568.

26. Meigs JB, Mittleman MA, Nathan DM, et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *Jama.* Jan 12 2000;283(2):221-228.
27. Pandolfi A, Giaccari A, Cilli C, et al. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta diabetologica.* 2001;38(2):71-76.
28. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. *Am J Med.* Apr 1991;90(4):450-459.
29. Herman WH, Ilag LL, Johnson SL, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes care.* Jul 2005;28(7):1568-1573.
30. Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. *Diabetes care.* Aug 2009;32(8):1513-1517.
31. Li FF, Zhang WL, Liu BL, et al. Management of glycemic variation in diabetic patients receiving parenteral nutrition by continuous subcutaneous insulin infusion (CSII) therapy. *Scientific reports.* Apr 12 2018;8(1):5888.