A Higher Serum Anion Gap is Associated with the Risk of Progressing to Impaired Fasting Glucose and Diabetes

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Research Article

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Abstract

Backgound Impaired fasting glucose (IFG) is an invertible interim hyperglycemia period with an increasing risk of diabetes and related complications. Our study was designed to identify that the serum anion gap is related to the risk of progressing to IFG and diabetes.

Methods We performed a prospective, population-based study among 1191 Chinese individuals aged 22-87 years who taken health examinations annually between 2006 and 2012 including clinical features and plasma metabolites. All of the participants had no history of diabetes or related chronic complications. We designed logistic regression analysis to examine the associations between clinical and metabolomic factors and the risk of developing to IFG or diabetes.

Results Among them, 58 subjects whose fasting glucose were between 6.1 and 7 mmol/L were diagnosed as IFG or diabetes. After adjusting for age, gender, body mass index (BMI), low-density lipoprotein (LDL), high-density lipoprotein (HDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), systolic blood pressure (SBP), diastolic blood pressure (DBP), potassium and albumin at baseline, the participants in the upper tertiles of serum anion gap (SAG) are more likely to progress to IFG or diabetes than those in the lower tertiles. Receiver operating characteristic (ROC) curve analysis was used to predict incidence of IFG or diabetes. We found the optimal cutoff level for the anion gap was 13.76 mmol/L and the AUC (area under ROC curve) was 0.623.

Conclusions Our data demonstrate that a higher SAG is associated with the risk of developing IFG or diabetes.

Introduction

Diabetes is actually a collection of metabolic illnesses that usually affect insulin secretion and uptake, with an increase in gluconeogenesis. In 2019, there were approximately 463 million patients at the age of 20–79 years suffering from diabetes globally, and the number is predicted up to 700 million by 2045[1]. Type 2 diabetes(T2DM), the most common type of diabetes, which imposes a considerable burden on society and patients[2]. Fortunately, T2DM can be prevented or delayed by targeting individuals at high risk[1]. IFG is prevalent and potentially reversible, which is an interim period between normal blood glucose condition and T2DM [3], and people with IFG have higher risk for progression to T2DM[3, 4] and concomitant complications[5]. Previous study demonstrated that about 9% of subjects with IFG will develop T2DM without intervention[6]. Identifying the clinical and molecular factors of IFG would enable a regression even reversal, from IFG to a normal glucose state, thereby reducing the incidence of diabetes.

A serum anion gap greater than 14 mmol/L is always considered to be abnormally elevated, and a gap of less than 6 mmol/L is considered to be abnormally low[7]. Previous studies showed that an elevated serum anion gap increased the risk for progression to severe kidney disease [8]. Lower serum bicarbonate is an indication that the SAG is high. We previously showed that people with a lower serum bicarbonate were more likely to progress to IFG and diabetes [9]. Other studies revealed that decreased serum

bicarbonate and increased SAG were related to insulin resistance[10], but no study has directly measured the effects of SAG on IFG or diabetes.

Since lower serum bicarbonate reflects higher SAG, we assume that higher SAG may predict the incidence of IFG or diabetes. In this study, we designed a perspective study to determine whether a higher serum anion gap may associate with the risk developing IFG or diabetes.

Material And Method

Study Subjects

The information of subjects who took physical examination in Beijing Tongren Hospital, Capital Medical University, Beijing, China were collected. Participants who underwent physical examinations and were followed up from 2006 to 2012. A total of 1191 individuals aged 22-87 were selected to take part in our study, whose fasting plasma glucose at baseline were at 3.9-5.5 mmol/L. Each participant visited the examination center every year for physical and laboratory examinations. Subjects with a history of diabetes, cancer, thyroid-related disease, or with previous history of usage of drugs that could affect acid and blood glucose at baseline or during the observation, and kidney, liver or other diseases related to glucose metabolism disorders were eliminated. The protocol was performed in accordance with the relevant guidelines and regulations. All subjects gave informed written consent to the research. This research was ratified by the Human Research Ethics Committee of Beijing Tongren Hospital (No. TRECKY2018-037).

Measurement of laboratory parameters

All participants in this research took health examinations, and their blood was sampled in the morning to ensure that the participants had fasted for more than 8 hours. Biochemical parameters, including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr) and fasting plasma glucose were measured by an automated chemistry analyzer (Beckman Coulter, CA, USA). Weight and height were measured by an MW-900A, Lejia, Hebei, China and were used to calculate body mass index (BMI) (kg/m^2). We used a standard questionnaire to evaluate history of drug use, acute and chronic illnesses. After resting for at least 5 minutes, let the subject sit and measure blood pressure by using an automatic blood pressure monitor (TM-2656VP, Aieande, Japan). Hypertension was defined as either systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg or the use of antihypertensive medications. The serum anion gap was calculated according to the equation as following: serum anion gap (mmol/L) =serum potassium level (mmol/L) + serum sodium level (mmol/L) - [serum chloride level (mmol/L) + serum bicarbonate level (mmol/L)].

Definition of progressing to IFG or diabetes

In 1997, the American Diabetes Association (ADA) defined diabetes as fasting plasma glucose ≥7.0 mmol/L and defined IFG as fasting plasma glucose ≥6.1 mmol/L and <7.0 mmol/L [11]. In our research, all of the subjects had a fasting plasma glucose between 3.9 and 5.5 mmol/L at baseline and were defined as having IFG or diabetes with a fasting plasma glucose ≥6.1 mmol/L (including ≥7.0 mmol/L) during the follow-up.

Statistical analysis

We stratified the participants into three groups by tertiles (lower, middle, and upper) according to serum anion gap levels at baseline. Clinical categorical variables were recorded in the form of percentages and frequencies. Quantitative variables are recorded as the means and standard deviations for normally distributed variables or medians and interquartile ranges for nonnormally distributed variables. The comparisons were tested between each group use one-way ANOVA for continuous variables and chi-square test for qualitative variables. The ORs of progression to IFG or diabetes were calculated by three logistic regression models. Variables that are possibly associated with IFG or diabetes and SAG levels are regarded as potential confounders to adjustment. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, sex, SBP, DBP, BMI, HDL and LDL. Model 3 was adjusted for age, sex, SBP, DBP, BMI, HDL, LDL, ALT, AST, K+ and albumin. The ROC curve of the SAG was analyzed in order to predict IFG or diabetes. The optimum cutoff point was used as the point with the plus sensitivity and maximum specificity. Moreover, the prevalence of IFG or diabetes was calculated by quintiles of the distribution of SAG. For all analyses, two-sided α level was considered as 0.05. All analyses were conducted using R-4.0.1 software version (http://www.r-project.org).

Results

Baseline Feature of the Research Subjects

A total of 1191 individuals, including 632 males and 559 females, carried out the follow-up in our research. We stratified all patients into three groups based on tertiles of their SAG values. The baseline characteristics are presented in Table 1. SAG values analyzed at the level from 2.30 to 24.54 mmol/L, with a mean ± SD (13.76 ± 2.96) mmol/L and median (IQR) 13.62 (3.82) mmol/L; the normal reference levels for serum anion gap were 6–14 mmol/L, and SAG > 14.1 mmol/L was considered to be a high level[12]. The participants with higher SAG levels were more prevalent in male and younger; and they also had higher weight, SBP, DBP, BMI, ALT, AST, LDL, K^+, ALB and lower HDL. After 6 years of follow-up, 58 individuals developed IFG/DM. Each group (serum anion nap low to high) had 10, 16 and 32 IFG/DM (Table 1).

Table 1
Baseline characteristics of participants by tertiles of serum anion gap

	By tertiles of serum anion gap			P value	Overall
	Low (≤ 12.51)	Middle (12.52–14.80)	High (≥ 14.81)		
n	397	397	397		1191
Age, years	34.6 (9.88)	32.7 (8.18)	30.7 (6.53)	< 0.0001	32.6 (8.46)
Sex					
Male	161 (40.6%)	209 (52.6%)	262 (66.0%)	< 0.0001	632 (53.1%)
Female	236 (59.4%)	188 (47.4%)	135 (34.0%)		559 (46.9%)
Hight, cm	166 (8.59)	169 (8.72)	170 (8.28)	< 0.0001	168 (8.65)
Weight, kg	64.1 (13.3)	67.4 (13.8)	69.2 (13.9)	< 0.0001	66.9 (13.8)
Body mass index, kg/m²	23.0 (3.46)	23.4 (3.56)	23.8 (3.65)	0.0053	23.4 (3.57)
Fasting blood glucose(mmol/L)	5.04 (0.33)	5.04 (0.34)	4.97 (0.34)	0.0016	5.02 (0.34)
Systolic blood pressure, mmHg	109 (12.5)	112 (12.1)	114 (12.7)	< 0.0001	112 (12.6)
Diastolic blood pressure, mmHg	71.0 (9.07)	73.4 (8.48)	75.6 (8.75)	< 0.0001	73.3 (8.96)
ALT, U/L	21.1 (16.8)	24.4 (17.7)	28.0 (20.6)	< 0.0001	24.5 (18.6)
K^+, mmol/L	4.13 (0.273)	4.19 (0.314)	4.23 (0.310)	< 0.0001	4.18 (0.302)
Ca^{2+}, mmol/L	2.37 (1.06)	2.36 (0.0808)	2.38 (0.0792)	0.89	2.37 (0.613)

Data are n (%) or mean (SD).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein;

* Fasting glucose (IFG)/ diabetes mellitus (DM)

	By tertiles of serum anion gap			P value	Overall
	Low (≤ 12.51)	Middle (12.52–14.80)	High (≥ 14.81)		
AST, U/L	25.3 (8.89)	26.5 (8.11)	28.6 (8.41)	< 0.0001	26.8 (8.58)
HDL, mmol/L	1.48 (0.361)	1.43 (0.367)	1.40 (0.357)	0.015	1.44 (0.363)
LDL, mmol/L	2.80 (0.688)	2.92 (0.829)	2.99 (0.700)	0.001	2.90 (0.744)
Albumin, g/L	43.4 (2.74)	44.3 (2.71)	45.5 (2.62)	< 0.0001	44.4 (2.82)
IFG/DM*					
Yes	10 (2.5%)	16 (4.0%)	32 (8.1%)	0.001	58 (4.9%)
No	387 (97.5%)	381 (96.0%)	365 (91.9%)		1133(95.1%)
Data are n (%) or mean (SD).					
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein;					
* Fasting glucose (IFG)/ diabetes mellitus (DM)					

The Association Between IFG or Diabetes Risk and the SAG by Logistic Regression Analysis

In logistic regression model 1, subjects in the upper tertiles of the serum anion gap had higher probability of incident IFG or diabetes than those in the lower tertiles first (OR 4.15, 95% CI 1.95 to 8.83; $p < 0.001$).

The ORs were still significant in models 2 (OR 3.77, 95% CI 1.75 to 8.1; $p < 0.001$) and model 3 (OR 3.44, 95% CI 1.55 to 7.59; $p < 0.001$) after adjusting for diverse variables. The subjects with serum anion gaps above the middle level had higher probability diagnosed as IFG or diabetes than those below the middle level (Table 2).

Table 2
Risk of fasting glucose (IFG)/ diabetes mellitus (DM) among individuals with higher serum anion gap, by different adjustment strategies, compared with that of individuals with lower serum anion gap

Model information	By tertiles of serum anion gap, OR (95% CI)			*p* value*
	Low (≤ 12.51)	Middle (12.52–14.80)	High (≥ 14.81)	
No. (%) of IFG/DM events	10 (2.5%)	16 (4.0%)	32 (8.1%)	-
Model1	1.00	1.67 (0.739, 3.75)	4.15 (1.95, 8.83)	0.00023
Model2	1.00	1.54 (0.681, 3.49)	3.77 (1.75, 8.1)	0.00069
Model3	1.00	1.54 (0.673, 3.52)	3.44 (1.55, 7.59)	0.0023
* High V.S. Low.				
Model 1: adjusted for age and sex.				
Model 2: model 1 + adjusted for body mass index, systolic blood pressure, Diastolic blood pressure, high-density lipoprotein (HDL) and low-density lipoprotein (LDL).				
Model 3: model 2 + adjusted for alanine aminotransferase (ALT), aspartate aminotransferase (AST), K^+ and Albumin.				

The Value of the SAG for Predicting the Incidence of IFG or Diabetes

The area under the ROC curve of the SAG to predict IFG or diabetes was 0.623 (95% CI 0.547 to 0.700). The sensitivity value of ROC curve analysis is 59.8%, specificity value of 50.8%. Negative predictive value (NPV) is 95.7% and the positive predictive value is 6.4%. The optimum cutoff value of SAG to predict IFG or diabetes was 13.76 mmol/L, which indicated that SAG was a predictor for the occurrence of IFG or diabetes (Fig. 1).

Next, we analyzed the occurrence of IFG or diabetes by the distribution of SAG values. Figure 2 shows the prevalence of IFG or diabetes by quintiles of the distribution of SAG. As the concentration of serum anion gap increased, the subjects suffering from IFG or diabetes were also increased (Fig. 2).

Discussion

In this prospective research, we observed that the prevalence of IFG or diabetes increased as the levels of SAG increased independent of risk factors such as age, sex, BMI, SBP, DBP, HDL, LDL, AST, ALT, potassium and albumin. The results of the ROC curve indicated that the SAG level had predictive ability

for the development of IFG or diabetes. In addition, the percentage of subjects progressing to IFG or diabetes increased as SAG increased.

Serum anion gap indicates the gap between undetermined cations and anions. This refers to the concentration of fixed acids in plasma, which is a normal used and easily gained laboratory parameter of acid-base imbalance[13]. The elevation of SAG is generally caused by the overproduction of organic acid anions and/or the concomitant and proportionate reduction in the anion excretions, while changes in the equivalents of potassium, calcium, phosphorus and total proteins are unusual causes[14]. It has been reported that lactate and ketoanions accounted for 62% of the increments in SAG[15].

In recent years, many researchs have revealed that elevated SAG is closely related to poor prognosis in various diseases, including acute and chronic kidney injury[8, 16], sepsis[17], acute pesticide poisoning[18], and coronary artery disease[19]. In a large study, it was shown that increased SAG may be of prognostic significance, as higher levels of AG were associated with hypertension[10].

In our research, men are more likely suffering from IFG or diabetes than women. Individuals with elevated SAG, both men and women, had a high probability of suffering from IFG. Poorer compliance and management in men with diabetes along with differences in the biological response to hyperglycemia and other risk factors between sexes[20, 21] may explain these findings. Obesity is a strong predictor of an increasing risk factor for adults T2DM[22, 23] and probably promote the development of diabetes[24]. Here, we show the participants in the upper tertiles of serum anion gaps had higher levels of weight and BMI, and these findings are consistent with previous studies. Lower HDL and higher LDL were also found in individuals with higher SAG. In recent studies, a high prevalence of IFG was significantly and independently related to increased LDL-C levels and low HDL-C levels[25, 26]. Dyslipidemia in this population indicates that obesity can affect the secretion of insulin and also may cause insulin resistance, which may explain this association[25].

Subjects with higher SAG had significantly higher SBP and DBP, and it was found in other studies that in prediabetic hypertensive patients, blood pressure control is less satisfactory than in nondiabetic patients[27, 28]. Furthermore, our study found that ALT, AST and albumin were higher as the SAG level increased. Previous studies also indicated a significant association between these parameters and IFG/DM[29, 30] because liver dysfunction related to chronic hepatitis or liver cirrhosis results in glucose intolerance[31].

In our study, the AUC of SAG was 0.623, suggested that the ability of SAG to discriminate IFG or diabetes was poor. This may be limited by our sample size. However, the NPV value was 95.7%, which suggested the predictive value for the absence of development of IFG or diabetes is great. The optimum cutoff value of SAG for predicting progression to IFG or diabetes was 13.76 mmol/L. This means that SAG above a certain level is harmful. We can see that the optimum cutoff value matches closely with the upper tertiles of the SAG level.

Although the precise mechanism underlying the association between SAG and IFG or diabetes risk has not been fully expounded, it may be related to insulin resistance, as a previous study has shown that high SAG was related to insulin resistance[10]. Ions play a very important role in maintaining homeostasis and regulating the electrical activities of pancreatic β-cells[32]. The Ca^{2+} influx and the depolarization of β-cells are caused by closure of ATP-sensitive potassium channels, which result in insulin granule exocytosis and insulin secretion[33]. SAG is related to several ion concentrations, so it may influence the occurrence of IFG through ions. The exact mechanism is still unclear and awaits further investigation and clarification.

However, the present study had three limitations. First, the sample size was small due to the withdrawal of the study halfway, and some participants did not undergo serological examinations. Thus, the number of patients who has a final diagnosis of IFG or type 2 diabetes was small, which may cause deviations in the results. Second, the study population was collected from one single clinical center, which may raise the possibility that the observed outcomes were specific to this peculiar patient population. Third, our adjustment for confounding variables may have been incomplete, including the consumption of medications and dietary variables that may influence blood glucose and the SAG level. However, we believe that these limitations do not bias the results of our study.

In a word, our study found that elevated SAG had higher odds of progressing to IFG or diabetes. Thus, possible proposals to encourage the general population to maintain normal SAG levels through diet or other methods may reduce the risk of developing IFG or diabetes. Controlling SAG at a relatively lower level may aid in the prevention of IFG or diabetes. Of course, large-scale, multicenter researches are necessary to confirm our results. Additional studies are required to discovery the exact underlying mechanism.

Declarations

Ethics approval and consent to participate

All experiments with laboratory animals were complied with the Ethical Review Committee at Beijing Tongren Hospital, Capital Medical University, China (No. TRECKY2018-037).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no duality of interest with the contents of this article.

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Author's Contributions

YcZ, JL and JkY conceived and designed the study; YcZ, FrX, RxZ and TtS analysed the data; all authors interpreted the data, drafted the article, revised it and approved the final version. JL and JkY is the guarantor of this work.

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Availability of data and material

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Ethics approval and consent to participate

All subjects gave informed written consent to the research. This research was ratified by the Human Research Ethics Committee of Beijing Tongren Hospital (No. TRECKY2018-037).

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Figures

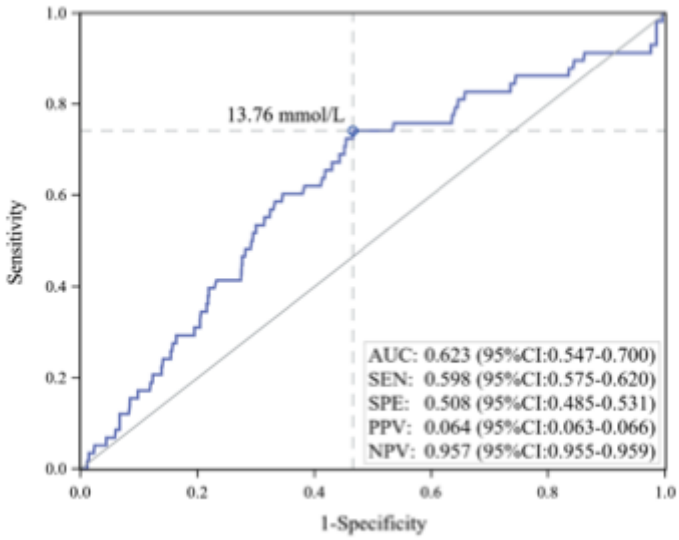

Figure 1

Receiver operating characteristic (ROC) curve of anion gap for predicting impaired fasting glucose (IFG)/ diabetes mellitus (DM). The optimal cut-off point for anion gap was 13.76 mmol/L.

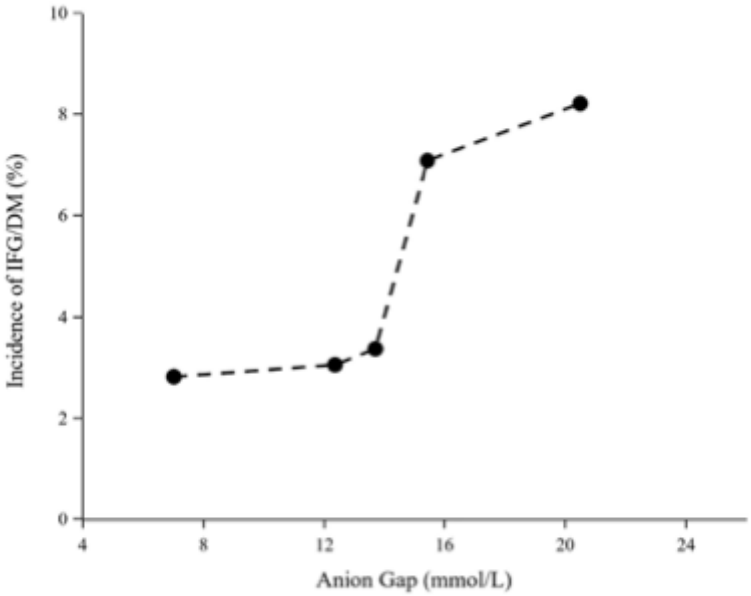

Figure 2

Prevalence of impaired fasting glucose (IFG)/ diabetes mellitus (DM) by different level the baseline serum anion gap.