A higher serum anion gap is associated with the risk of progressing to impaired fasting glucose and diabetes

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Research

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Abstract

Impaired fasting glucose (IFG) is a reversible interim hyperglycemic period in which there is an increasing risk of developing diabetes and related complications. Our study aimed to identify that serum anion gap is related to the risk of IFG and diabetes development. We performed a prospective, population-based study among 1191 Chinese individuals aged 22–87 years who underwent health examinations annually between 2006 and 2012 including determining clinical biochemistry and plasma metabolite parameters. All the participants had no history of diabetes or related chronic complications. We performed logistic regression analysis to examine the association between clinical and metabolomic factors and the risk of developing IFG or diabetes. Among them, 58 subjects whose fasting glucose level was between 6.1 and 7 mmol/L were diagnosed with IFG or diabetes. After adjusting for age, sex, body mass index (BMI), low-density lipoprotein (LDL), high-density lipoprotein (HDL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, systolic blood pressure (SBP), diastolic blood pressure (DBP), potassium and albumin (ALB) levels at baseline, the participants in the upper tertiles of serum anion gap (SAG) were more likely to develop IFG or diabetes than those in the lower tertiles. Receiver operating characteristic (ROC) curve analysis was used to predict the 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. Our data demonstrates that a higher SAG is associated with the risk of developing IFG or diabetes.

Introduction

Diabetes is a group of metabolic illnesses that is characterized by defects in insulin secretion and uptake and increased gluconeogenesis. In 2019, approximately 463 million individuals globally in the age range of 20–79 years developed diabetes and this number is predicted to increase to up to 700 million by 2045[1]. Type 2 diabetes (T2DM), the most common type of diabetes, imposes a considerable economic burden on the society and patients[2]. Fortunately, T2DM can be prevented or delayed by targeting high-risk individuals[1]. Impaired fasting glucose (IFG), a type of pre-diabetic condition, is an interim period between the condition of normal blood glucose level and full-blown T2DM[3]. IFG is prevalent among high-risk individuals but is potentially reversible. However, people with IFG have higher risk for progression to T2DM[3, 4] and concomitant complications[5]. A previous study demonstrated that about 9% of individuals with IFG will develop T2DM without intervention[6]. Therefore, identifying the clinical and molecular factors associated with IFG development would enable regression or even reversal of IFG to the normal state, thereby reducing the incidence rate of T2DM.

A serum anion gap (SAG) greater than 14 mmol/L is considered to be an abnormally increased value, whereas a gap of less than 6 mmol/L is considered to be abnormally low[7]. A previous study showed that an increased serum anion gap increased the risk for the development of chronic kidney disease[8]. Lower serum bicarbonate level is an indication that the SAG is high. We previously showed that individuals with a low serum bicarbonate level were more likely to develop IFG and diabetes[9]. Another study reported that decreased serum bicarbonate level and increased SAG were related to insulin
resistance[10] but no study has directly measured the effects of SAG on the development of IFG or diabetes.

Since low serum bicarbonate level indicates higher SAG, we assumed that higher SAG may predict the incidence of IFG or diabetes. Therefore, we designed a perspective study to determine whether a high serum anion gap may be associated with the risk of developing IFG or diabetes.

**Material And Methods**

**Study Subjects**

The information of subjects who underwent physical examination at Beijing Tongren Hospital, Capital Medical University, Beijing, China were collected and those who had undergone the physical examination from 2006 to 2012 were followed. A total of 1191 individuals aged 22–87 years whose fasting plasma glucose level at baseline was in the range of 3.9–5.5 mmol/L were selected. Each participant visited the examination center every year for physical and laboratory examinations. Subjects with a history of diabetes; cancer; thyroid-related disease; a previous history of taking medication that could affect acid and blood glucose level at baseline or during the observation; or kidney, liver, or other diseases related to glucose metabolism were excluded. All the subjects gave informed written consent to the research. This research was certified by the Human Research Ethics Committee of Beijing Tongren Hospital (No. TRECKY2018-037).

**Measurement of laboratory parameters**

All participants underwent health examinations, and their blood samples were collected in the morning to ensure that they had fasted for more than 8 hours. Biochemical parameters including triglyceride (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 levels were measured using an automated chemistry analyzer (Beckman Coulter, CA, USA). Weight and height were measured using MW-900A (Lejia, Hebei, China) and the values were used to calculate body mass index (BMI) (kg/m²). We used a standard questionnaire to obtain information about the history of medication use, and acute and chronic illnesses. After resting for at least 5 min, the subject was allowed to sit and the blood pressure was measured using an automatic blood pressure monitor (TM-2656VP, Aieande, Japan). Hypertension was defined as a systolic blood pressure (SBP) of $\geq$140 mm Hg, diastolic blood pressure of (DBP) of $\geq$90 mm Hg, or the use of antihypertensive medications. The serum anion gap was calculated according to the following equation: 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) considered as a fasting plasma glucose level of $\geq 7.0$ mmol/L as a hallmark for diabetes and a fasting plasma glucose level of $\geq 6.1$ mmol/L and $< 7.0$ mmol/L as a hallmark for IFG [11]. In our study, all the subjects had a fasting plasma glucose level between 3.9 and 5.5 mmol/L at baseline. Those with a fasting plasma glucose of $\geq 6.1$ mmol/L (including $\geq 7.0$ mmol/L) during follow-up were considered to have IFG or diabetes.

Statistical analysis
We classified the participants into three groups by tertiles (lower, middle, and upper) according to their serum anion gap levels at baseline. Clinical categorical variables were recorded in the form of percentages and frequencies. Quantitative variables were recorded as the means and standard deviations for normally distributed variables or medians and interquartile ranges for discrete variables. The comparisons were tested between each group use one-way analysis of variance 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 were possibly associated with IFG or diabetes and SAG was considered a potential confounder 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 SAG was analyzed 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, a two-sided $\alpha$ value of 0.05 was considered. All analyses were performed using R-4.0.1 software version (http://www.r-project.org).

Results
Baseline Characteristics of the Subjects
A total of 1191 individuals, including 632 males and 559 females, were followed up in our study. We classified all the patients into three groups based on the tertiles of their SAG values. The baseline characteristics are presented in Table 1. SAG values were 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 an SAG value of $> 14.1$ mmol/L was considered high[12]. Male and younger participants had higher SAG in addition to higher weight, SBP, DBP, BMI, ALT, AST, LDL, $K^+$, and ALB levels and lower HDL levels. After 6 years of follow-up, 58 individuals developed IFG/DM. Each group (serum anion gap low to high) had 10, 16, and 32 IFG/DM patients (Table 1).
| 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) |
| Ca²⁺, 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%) |

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

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

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

**Association between IFG or Diabetes Risk and SAG According to Logistic Regression Analysis**

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

The ORs were significant in model 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 a higher probability of developing 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.

Using SAG for Predicting the Incidence of IFG or Diabetes

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

Next, we analyzed the development of IFG or diabetes based on the distribution of SAG values. Figure 2 shows the prevalence of IFG or diabetes by quintiles of the distribution of SAG values. As the concentration of serum anion gap increased, the number of subjects with IFG or diabetes also increased (Fig. 2).

Discussion

In this prospective study, 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, K+, and ALB levels. The results of the ROC curve indicated that SAG had the ability to predict 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 the levels of undetermined cations and anions. This refers to the concentration of fixed acids in the plasma, which is a normally used and easily determinable laboratory parameter signifying acid–base imbalance[13]. An increase in SAG is generally caused by the overproduction of organic acid anions and/or the concomitant and proportionate reduction in 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 the recent years, many studies have reported that increased 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, increased SAG was considered to be of prognostic significance, as higher levels of AG were associated with hypertension[10].

In our study, men were more likely to develop IFG or diabetes than women. Individuals with increased SAG, both men and women, had a high probability of developing 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 adult-onset T2DM[22, 23] and probably promote the development of diabetes[24]. Here we showed that the participants in the upper tertiles of serum anion gaps were overweight and had high BMI values, and these findings are consistent with those of previous studies. Lower HDL and higher LDL levels were also found in subjects with higher SAG. In a few recent studies, the 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 may also 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 levels were higher as the SAG increased. Previous studies also indicated a significant association between these parameters and the development of IFG/T2DM[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 SAG cannot be used to distinguish between IFG and diabetes. This observation may have been caused by our limited sample size. However, the NPV value was 95.7%, which suggested that the predictive value for the absence of development of IFG or diabetes is high. 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 matched closely with the upper tertiles of the SAG.

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 showed 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\textsuperscript{2+} influx and depolarization of β-cells are caused by closure of ATP-sensitive potassium channels, which result in insulin granule exocytosis and secretion[33]. SAG is related to several ion concentrations, so it may affect the development 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 because of the abrupt withdrawal from the study by some of the participants and some participants did not undergo serological examinations. Thus, the number of patients who underwent IFG or T2DM diagnosis was small, which may have caused deviations in the results. Second, the study population was included from a single clinical center, which may lead to 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 affect blood glucose level and SAG. However, we believe that these limitations do not contribute to a bias in the results of our study.

**Conclusion**

In summary, our study found that individuals with increased SAG had a higher chance of developing IFG or diabetes. Thus, possible strategies to encourage the general population to maintain normal SAG 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 studies are necessary to confirm our results and determine the underlying mechanism.

**Abbreviations**

IFG Impaired fasting glucose

BMI Body mass index

LDL Low-density lipoprotein

HDL High-density lipoprotein

ALT Alanine aminotransferase

AST Aspartate aminotransferase

SBP Systolic blood pressure

DBP Diastolic blood pressure,

SAG Serum anion gap

ROC Receiver operating characteristic
T2DM Type 2 diabetes
TG Triglyceride
TC Total cholesterol
Cr Serum creatinine
ADA American Diabetes Association
NPV Negative predictive value
ALB Albumin
AUC Area under ROC curve

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).

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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.