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ARTICLE

Inverse association between fasting plasma glucose and risk of ventricular arrhythmias

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Abstract
Aims/hypothesis In nondiabetic individuals, low values of fasting plasma glucose (FPG) have been associated with an increased risk of cardiovascular events. Identification of the potential mechanisms behind this association could help to elucidate the relationship between glycaemia and cardiovascular disease. We aimed to determine the association between FPG and ventricular arrhythmias.
Methods FPG and other cardiometabolic risk factors were measured in a population-based cohort of 2,482 men without a known history of type 2 diabetes mellitus at baseline. Associations between FPG levels and incident cases of ventricular arrhythmias (ventricular tachycardia or fibrillation events ascertained using the National Hospital Discharge Register) were estimated using Cox regression analysis adjusted for potential confounders.
Results During a median follow-up of 23.3 (interquartile range 18.5–25.3) years, 74 (2.9%) incident events were recorded. In a multivariable analysis adjusted for age, systolic BP, smoking status, LDL- and HDL-cholesterol, and C-reactive protein, the HR for ventricular arrhythmia per 1 mmol/l higher baseline FPG was 0.58 (95% CI 0.34, 0.98); this estimate did not materially change after further adjustment for BMI, alcohol consumption, triacylglycerols and history of ischaemic heart disease (0.50 [95% CI 0.28, 0.89]).
Conclusions/interpretation In this nondiabetic male population, FPG was inversely associated with incident risk of ventricular arrhythmias. While our results could help clarify the relationship between low glucose levels and cardiovascular risk, further studies are required to confirm these findings in other populations.

Keywords Blood glucose · Cardiac arrhythmias · Cardiovascular diseases · Cox models · Observational study

Abbreviations

FPG	Fasting plasma glucose
KIHD	Kuopio Ischaemic Heart Disease
NIHR	National Institute for Health Research
SCD	Sudden cardiac death

Introduction

Large, prospective observational studies have demonstrated a 'J-shaped' relationship between fasting plasma glucose (FPG) and major cardiovascular events in nondiabetic individuals [1–5]. While increased risk associated with higher values of FPG is commonly considered to be related to more severe atherosclerosis, the link between lower FPG values and the risk of cardiovascular events is not fully understood. It has been proposed that a lower FPG could be a marker of conditions associated with an increased risk [1, 6]; however, this hypothesis has not been proven.

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Cardiac rhythm disturbances (ventricular arrhythmias, in particular) are considered to be the final events in a chain of complications leading to cardiac death from atherothrombotic occlusion of coronary arteries [7]. However, arrhythmic abnormalities can be also caused by hypoglycaemia [8–10], potentially explaining the lack of a reduction in fatal events in a randomised clinical trial of intensively treated type 2 diabetic patients [11].

To help clarify these epidemiological and clinical trial observations, we evaluated the association between FPG and risk of incident ventricular tachycardia or fibrillation in a general male population (i.e. not selected on the basis of pre-existing disease) who participated in the Kuopio Ischaemic Heart Disease (KIHD) prospective study [12].

Methods

This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology [13].

Setting and participants The KIHD study was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland; details of the study have been reported previously [12]. Participants comprised a randomly selected sample of 3,433 men aged 42–60 years who were resident in the town of Kuopio or its surrounding rural communities; baseline examinations were conducted between 1984 and 1989. Of those invited, 2,682 (78.1%) participated in the study. After the exclusion of 162 individuals with prevalent diabetes (either undergoing regular treatment with an oral hypoglycaemic agent or insulin therapy or undergoing dietary treatment only [those with a FPG level of at least 7.0 mmol/l]) and of 38 with missing information about FPG, 2,482 participants were included in the analyses.

Blood samples and measurements were taken between 08:00 and 10:00 hours. In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days and from smoking for at least 12 h prior to testing. A glucose dehydrogenase method (Merck, Darmstadt, Germany) was used to measure blood glucose after protein precipitation by trichloroacetic acid. HDL was separated from fresh samples by ultracentrifugation and precipitation; the next day, the cholesterol content of lipoprotein fractions and serum triacylglycerols were measured enzymatically (Boehringer Mannheim, Mannheim, Germany). Serum creatinine concentrations were measured by the colorimetric Jaffe method using a Konelab 20XT automatic analyser (Thermo Fisher Scientific, Espoo, Finland). Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA).

Resting systolic BP was measured with a random zero sphygmomanometer (Hawksley, Lancing, UK) by two trained nurses using the following protocol: after supine rest of 5 min, three measurements were made in a supine position, followed by one in a standing position and two in a sitting position at 5 min intervals. Systolic BP was taken as the mean of all six measurements [14]. Baseline diseases, smoking habits and years of education were assessed by self-administered questionnaires. The diagnosis of chronic diseases was checked during a medical examination by an internist. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory [14]. BMI was calculated as the ratio of weight in kilograms to the square of height in metres.

Ethical approval for the study was obtained from the Research Ethics Committee of the University of Eastern Finland. All participants gave written informed consent.

Outcomes and follow-up All patients with incident ventricular tachycardia or fibrillation that occurred from study baseline (March 1984–December 1989) through 2012 were included. Annually updated data on new incident outcome events were obtained by a computer linkage to the National Hospital Discharge Register, and International Classification of Diseases (9th Revision [ICD-9]; 427.41) or ICD-10 (I47.2, I49.0) codes were used to define ventricular arrhythmias. The definition of non-sustained or sustained ventricular tachycardia and/or ventricular fibrillation was based on electrocardiography. Documents were cross-checked in detail by two physicians, and an independent events committee blinded to the clinical data classified the outcomes [15]. There were no losses during follow-up.

Statistical analysis For all the analyses, natural logarithm transformed values of non-normal distributed variables (C-reactive protein, triacylglycerols and alcohol consumption) were used. Descriptive data are presented as means±SD for continuous variables and numbers and percentages for categorical variables; differences were estimated with ANOVA and the χ^2 test, respectively.

Cox regression modelling was used for analysing associations between FPG and the outcomes involved. The proportional hazards assumption was verified for all variables by inspecting the plots of the Schoenfeld residuals for covariates. HRs were estimated within FPG quartiles relative to the bottom quartile against the mean FPG level in each quartile; 95% CIs were estimated from variances attributed to the groups to reflect the amount of information within each group (including the reference category [16]). To assess the independence of association between FPG and incident ventricular arrhythmia, we calculated HRs by quartiles and per 1 mmol/l higher baseline FPG, with progressive adjustment for potential confounders selected on the basis of their previously established role as predictive cardiovascular risk factors.

Two-sided analyses were performed using Stata version 13 (StataCorp, College Station, TX, USA), and CIs are presented at the 95% level.

Results

At baseline, 32% were smokers, the mean (± SD) age was 53 (±5) years and the mean FPG was 4.6 (±0.5) mmol/l. Baseline characteristics of the study participants by quartile of FPG are reported in Table 1. With the exception of systolic BP and triacylglycerols, levels of cardiometabolic risk factors were not significantly different in individuals who had an arrhythmic event throughout follow-up compared with those who had not (electronic supplementary material [ESM] Table 1). During a median follow-up period of 23.3 (interquartile range 18.5–25.3) years, there were 152 (6.1%) cases of diabetes (risk factors are shown in ESM Table 2), 318 (12.8%) of fatal CHD events and 74 (2.9%) of ventricular arrhythmias, with a crude incidence rate of 1.43 (95% CI 1.14, 1.80) per 1,000 person-years.

The relationship between a 1 mmol/l higher baseline FPG and incident ventricular tachycardia or fibrillation events, adjusted for potential confounders, is reported in Table 2 (HRs by FPG quartiles are shown in ESM Table 3). In the analysis adjusted for age, SBP, current smoking, LDL- and HDL-cholesterol, and C-reactive protein, a 1 mmol/l higher baseline FPG was associated with a HR of 0.58 (95% CI 0.34, 0.98) of ventricular arrhythmic events; further progressive adjustment for BMI, alcohol consumption, triacylglycerols and history of ischaemic heart disease at baseline did not materially change the estimate (Table 2, Fig. 1). Similarly, the additional inclusion of GFR, use of β-blockers, and serum sodium and potassium levels resulted in comparable associations (Table 2; ESM Table 3).

Discussion

Our results suggest that, in a general male population, lower FPG levels are associated with a higher risk of ventricular tachycardia/fibrillation independent of other cardiovascular risk factors.

Although nondiabetic hyperglycaemic states have been associated with major vascular events, the precise relationship between FPG and cardiovascular outcomes remains unclear. Indeed, graded continuous [17, 18], threshold [19], and 'J-shaped' [1–5] relationships have been reported. The reasons behind these divergent patterns are unclear, and may relate to different study characteristics and methods, or be due to inherent diversity in the participants. In studies showing a 'J-shaped' association, the nadir has been variously reported as between 3.3 and 5.6 mmol/l; moreover, it has been suggested that low glucose values could be a marker of conditions associated with an increased risk of vascular events, such as liver or kidney dysfunction [20]; however, this hypothesis has not yet been clearly proven.

On the other hand, experimental studies have shown that low plasma glucose levels can cause ventricular electrophysiological abnormalities (i.e. QT interval prolongation) associated with an increased risk of ventricular arrhythmias in both diabetic and nondiabetic individuals [8–10]. Hypoglycaemia can increase the risk of ventricular arrhythmias through direct (e.g. the effect of low glucose on ion channel activity [21]) and indirect (e.g. hypokalaemia, catecholamine release) mechanisms. However, no study has prospectively demonstrated a link between FPG and the risk of ventricular arrhythmic events in a nondiabetic population.

These results have important ramifications. First, although large epidemiological studies tend to combine outcomes, the heterogeneity of mechanisms that eventually result in what is collectively (and simplistically) classified as a single outcome is being increasingly recognised for both cardiovascular [22, 23] and other diseases [24, 25]. Our results could suggest that, across the range of FPG levels, increased risk at the upper and lower extremities could be attributable to different pathophysiological pathways leading to the same defined outcome. We consider that a better definition of the multiple mechanisms driving cardiovascular disease outcomes is essential.

Second, our findings could help interpret recent trials of patients with type 2 diabetes mellitus. While early studies demonstrated a reduction in major vascular events associated with glucose control, more recent studies with near-to-normal glucose targets have shown a nonsignificant reduction or even an increase in vascular risk in intensively treated participants [11]. Although controversial, hypoglycaemia has been considered a potential explanation [26], and an increased specific risk of arrhythmic death has been associated with severe hypoglycaemia in a post hoc trial analysis [27]. Indeed, the increasingly recognised risk associated with hypoglycaemic events has driven the European Medicines Agency to adopt a higher blood glucose level cut-off value (3.9 mmol/l) to define hypoglycaemia [28], in line with the ADA and Endocrine Society consensus report [29]. From this perspective, our results would support hypoglycaemia as a plausible mechanism that could contribute to increased cardiovascular mortality during intensive glycaemic therapy.

In a previous analysis exploring the association between FPG and sudden cardiac death (SCD) in nondiabetic individuals from the general population, a positive relationship was found [30]. Notably, of 190 SCD events that occurred during follow-up, 157 were out-of-hospital events; therefore, for the large majority of events (82.6%) it was not possible to assess the presence of ventricular arrhythmias. While SCD is generally considered to be the consequence of ventricular fibrillation/tachycardia, it is also well-known that SCD can also have

Table 1 Baseline characteristics of the study participants (N=2,482) by quartile of FPG

Characteristic	FPG quartiles (min–max) (mmol/l)				
	1st (3.2–4.3)	2nd (4.4–4.5)	3rd (4.6–4.9)	4th (5.0–6.2)	p value for trend
Sample size, % (n)	32.4 (804)	19.0 (473)	28.4 (704)	20.2 (501)	–
Age (years)	52.7 (5.2)	53.0 (5.1)	53.2 (5.0)	53.0 (5.1)	0.137
BMI (kg/m^2)	25.6 (3.1)	26.7 (3.1)	27.0 (3.3)	27.9 (3.8)	<0.001
Systolic BP (mmHg)	131 (16)	134 (17)	134 (17)	137 (17)	<0.001
LDL-cholesterol (mmol/l)	3.99 (0.99)	4.05 (1.04)	4.10 (1.02)	4.04 (1.00)	0.135
HDL-cholesterol (mmol/l)	1.32 (0.32)	1.29 (0.28)	1.30 (0.30)	1.28 (0.30)	0.055
Triacylglycerols[a] (mmol/l)	1.02 (0.76–1.40)	1.11 (0.79–1.54)	1.17 (0.79–1.54)	1.18 (0.83–1.76)	<0.001
FPG (mmol/l)	4.1 (0.2)	4.4 (0.1)	4.7 (0.1)	5.3 (0.3)	<0.001
Sodium (mmol/l)	140.9 (1.4)	140.8 (1.5)	140.8 (1.5)	140.6 (1.7)	0.001
Potassium (mmol/l)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	0.777
GFR[b] (ml/min/1.73 m^2)	78 (13)	79 (14)	79 (13)	81 (18)	<0.001
High sensitivity C-reactive protein[a] (mg/l)	1.17 (0.63–2.24)	1.23 (0.70–2.33)	1.25 (0.73–2.27)	1.55 (0.81–2.83)	<0.001
Alcohol consumption[a] (g/week)	27 (6–76)	37 (5–88)	25 (5–90)	43 (7–121)	0.008
Previously diagnosed diseases					
Current smoking	33.9 (273)	33.8 (160)	29.5 (208)	32.1 (161)	0.192
Ischaemic heart disease	24.0 (193)	20.9 (99)	25.4 (179)	25.7 (129)	0.283
Hypertension	25.1 (202)	28.2 (133)	30.3 (212)	28.8 (165)	0.001
Heart failure[c]	4.6 (37)	6.7 (32)	7.6 (53)	8.2 (41)	0.006
Cerebrovascular disease	2.1 (17)	2.5 (12)	0.8 (6)	2.9 (15)	0.915
Claudication	3.4 (27)	2.9 (14)	4.8 (34)	4.2 (21)	0.191
Pulmonary diseased	13.3 (95)	14.2 (60)	14.6 (94)	12.4 (56)	0.905
Cancer	1.9 (15)	1.9 (9)	1.9 (14)	1.6 (8)	0.822
Regular use of medication					
Antidyslipidaemic	0.8 (7)	0.2 (1)	0.4 (3)	0.9 (5)	0.967
Antihypertensive	18.8 (151)	18.4 (87)	22.1 (156)	24.7 (124)	0.005
β-blockers	14.8 (119)	14.4 (68)	18.6 (131)	19.9 (100)	0.004
Acetylsalicylic acid	7.6 (61)	4.9 (23)	7.5 (53)	8.4 (42)	0.453
Incident events					
Fatal CHD	11.6 (93)	12.0 (57)	11.4 (80)	17.6 (88)	0.012
Type 2 diabetes mellitus	2.5 (20)	4.2 (20)	6.7 (47)	12.9 (65)	<0.001

Unless otherwise stated, data are means (SD) for continuous variables and as % (n) for categorical variables

[a] Data are median (interquartile range)

[b] Estimated with the Modification of Diet in Renal Disease formula: $175 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203}$; diagnosis based on clinical findings and symptoms and/or echocardiography

[c] Including bronchial asthma, chronic obstructive pulmonary disease and pulmonary tuberculosis

other causes, and that only about 50% of SCD events are attributable to ventricular fibrillation/tachycardia [31]. This could explain the divergence in the relationship between FPG-related SCD and FPG-related ventricular arrhythmias,

Table 2 HR of ventricular tachycardia/fibrillation per 1 mmol/l higher baseline FPG

Level of adjustment	HR (95% CI)	p value
Age, SBP, smoking, LDL-chol, HDL-chol, C-reactive protein	0.58 (0.34, 0.98)	0.042
Above + BMI, alcohol consumption, triacylglycerols	0.50 (0.28, 0.89)	0.019
Above + history of ischaemic heart disease	0.50 (0.28, 0.89)	0.020
Above + eGFR, β-blockers use	0.51 (0.28, 0.92)	0.025

Chol, cholesterol; eGFR, estimated GFR; SBP, systolic BP

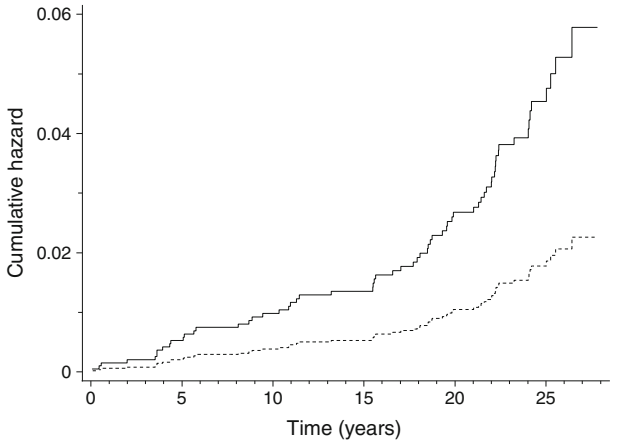

Fig. 1 Cumulative hazard for ventricular arrhythmias, comparing quartiles of baseline FPG. HR for higher (dotted line) vs lower (solid line) quartile of FPG: 0.39 (95% CI 0.19, 0.78), adjusted for age, systolic BP, LDL- and HDL-cholesterol, smoking status, C-reactive protein, BMI, alcohol consumption, triacylglycerols and prevalent ischaemic heart disease. Range for FPG quartiles: lower, 3.2–4.3 mmol/l; higher, 5.0–6.2 mmol/l

and further underlines the need to identify the multiple mechanisms responsible for cardiovascular outcomes.

We should acknowledge some limitations of this study. First, generalisation of our findings is limited by the study population, which consists of only middle-aged Finnish men; these results therefore need to be confirmed in other ethnic groups. Second, no information on the nature of the ventricular arrhythmic events was recorded. Third, identification of an association does not necessarily indicate a cause–effect relationship between FPG and arrhythmic disorders. Although experimental studies would support this, low FPG could be a confounder of a condition that increases the risk of ventricular arrhythmias. Fourth, the independence of the association between FPG and ventricular arrhythmias was assessed by adjusting for several well-known potential confounders, including drugs for hypertension and dyslipidaemia; however, baseline data on other specific medications (e.g. diuretics) were not available. On the other hand, the strengths of this study include the rigorous measurement of baseline risk factors and the assessment of ventricular arrhythmias, the large, homogeneous community-based sample and the long follow-up period.

In conclusion, in this nondiabetic male population, FPG was inversely associated with an incident risk of ventricular arrhythmias. Further studies are warranted to confirm these results in other populations to help clarify the complex association between glucose and cardiovascular disease.

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Duality of interest KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme; received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme; has received funds for research and honoraria for speaking at meetings; and served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk. MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation; and received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement FZ designed the study, analysed the data and drafted the manuscript. DRW, KK and MJD interpreted the data and drafted and critically revised the manuscript for important intellectual content. SK acquired and interpreted the data, and drafted the manuscript. JAL designed the study, interpreted the data, and drafted and critically revised the manuscript for important intellectual content. FZ had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version to be published.

The manuscript represents valid work and neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere. Data are available on request from the corresponding author.

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