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Impaired glucose tolerance as a risk factor for stroke in a cohort of non-institutionalised people aged 70 years

MINNA M. KAARISALO, ISMO RÄIHÄ, SEIJA ARVE, AAPO LEHTONEN

Turku City Hospital, Turku, Finland

Address correspondence to: M. M. Kaarisalo, Kylliäisentie 32, 21620 Kuusisto, Finland. Fax: (+358) 2 2385 692.
Email: minna.kaarisalo@utu.fi

Abstract

Objective: to determine whether impaired glucose tolerance (IGT) is associated with an increased likelihood for ischaemic stroke.
Design: prospective cohort study.
Participants: a sample of 1,032 non-institutionalised people aged 70 years in the Turku Elderly Study, Turku, Finland.
Measurements: the association between IGT (defined as plasma glucose level between 7.80 and 11.09 mmol/l 2 h after administration of 75 g of an oral glucose load) and diabetes mellitus (DM) (defined as the current use of insulin or an oral hypoglycaemic medication, a fasting plasma glucose level of ≥7 mmol/l or a plasma glucose level of ≥11.1 mmol/l 2 h after administration of an oral glucose load) with 12-year follow-up for the development of ischaemic stroke.
Results: a total of 742 (71.9%) subjects had normal glucose tolerance, 127 (12.3%) subjects had IGT and 163 (15.8%) had DM. Patients were examined in the year 1990 and followed up for stroke occurrence until death or until the end of 2002. Mean follow-up time was 9.6 years (SD ±3.3 years). In total, 119 patients (11.5%) suffered a stroke during the follow-up. In logistic regression model, previous stroke, previous TIA, DM and atrial fibrillation were risk factors for stroke occurrence.
Conclusion: stroke tended to happen more often in the IGT group than in the normal group, but the difference was not statistically significant. Statistically significant risk factors for stroke in elderly people are previous TIA or stroke, DM and atrial fibrillation.

Keywords: *impaired glucose tolerance, ischaemic stroke, risk, elderly*

Introduction

Glucose abnormalities have their highest prevalence and their greatest impact on the health of the elderly population [1]. Data from several prospective studies in non-diabetic adults have yielded inconsistent findings on the relationship between impaired glucose tolerance (IGT) and cardiovascular disease (CVD) risk. They have suggested various associations, including flat, J-shaped, linear and threshold relationships for various glucose measures and cardiovascular outcomes [2–7]. Previous studies have usually pooled coronary heart disease and stroke mortality together, and studies regarding IGT and stroke exclusively are scarce. Although some studies have identified IGT as an independent and significant risk factor for stroke or stroke mortality [3, 6, 8], in other studies IGT did not persist as an independent risk factor for stroke in the multivariate analysis [9–11].

The purpose of this report is to describe the prevalence of IGT among elderly men and women and to determine whether IGT predisposes persons to non-fatal and fatal strokes.

Study population and methods

Study population

The Turku Elderly Study sample represents 70-year-old home-dwelling citizens of the city of Turku. The sample was part of a population-based ageing study of three urban areas in southern Finland. The age cohort of 70-year-old inhabitants of the city was examined in 1990. The purpose

of the examination was to define the health of the 70-year-olds and thus to forecast the future need and use of health care services. The age cohort comprised of 1,503 persons. Of these, 264 were institutionalised and therefore excluded. Of the 1,239 home-dwelling citizens in the base line, 143 refused to take part and 64 persons could not be contacted. Thus, the final sample consisted of 1,032 persons.

Methods

The basic study data were collected in the first stage of the survey by mail using a structured seven-page questionnaire. After this, a public health nurse did a structured interview, and thereafter a local health care physician reviewed all available patient records and performed a thorough clinical examination with ancillary tests if needed. Comprehensive laboratory investigations in the fasting state (among other things haemoglobin sedimentation rate, haemoglobin, total and high-density lipoprotein (HDL) cholesterol, triglycerides, serum glucose and insulin values and electrocardiogram) were carried out, and if the person did not have diabetes mellitus (DM), then also an oral post-challenge glucose test with 75 g glucose was included.

Subjects who had a history of diabetes were classified as having previously diagnosed diabetes. In Finland, all antidiabetic medication is free of charge, but a patient must first submit a thorough doctor's statement for the Social Insurance Institution's register for free-of-charge medications. The diagnosis of DM follows the 1999 World Health Organization (WHO) recommendations for the diagnosis of diabetes [12]. For quality control purposes, 27% of these previously diagnosed DM patients underwent a glucose tolerance test, and the previous diagnosis of DM was found to be accurate. IGT was defined as plasma glucose level of between 7.80 and 11.09 mmol/l 2 h after administration of 75 g of an oral glucose load. DM was defined as the current use of insulin or an oral hypoglycaemic medication, a fasting plasma glucose level of ≥7.0 mmol/l or a plasma glucose level of ≥11.1 mmol/l 2 h after administration of an oral glucose load.

The occurrence of cerebrovascular disorders (ICD-9 codes 430–436 and ICD-10 codes I60–I69) was mainly found by follow-up examination of the Turku Elderly Study cohort in the year 2000. For the patients who died during the follow-up ($n = 310$) or refused to take part in the follow-up examination at the age 80 years ($n = 121$), the Hospital Discharge Register and the National Death Register were used. For the years 2000–2002, only the Hospital Discharge Register and the National Death Register were used. Most patients with symptoms and clinical signs suggestive of acute stroke are hospitalised in Finland [13].

The city of Turku was one of the WHO MONICA's reporting units and participated in the MONICA study for years 1983–1992 [14]. Only in the Turku reporting unit were all stroke patients registered without an upper age limit during the whole FINMONICA study period, even though the age range in the core WHO MONICA Stroke Study was 25–75 years; 1993–1998 stroke registration was carried on in the FINSTROKE register [15]. For quality control purposes, we did a computerised linkage of FINMONICA and FINSTROKE registers for the years 1990–1998, but no additional stroke cases were found.

Haemorrhagic strokes represented only 10% ($n = 13$) of the strokes. This is in concordance with 13% of haemorrhagic strokes in the Cardiovascular Health Study [7]. Because diabetes is a risk factor primarily for the ischaemic stroke and not necessarily for haemorrhagic strokes [16], we excluded haemorrhagic strokes from our present analyses.

The Turku Elderly Study register consisted of 679 variables. For this study, we selected variables that have been identified as risk factors for stroke in previous studies of middle-aged populations. The following risk factors were included in the analyses: sex, prior stroke, prior transient ischaemic attack (self-reported or diagnosis in previous medical records), atrial fibrillation, a history of myocardial infarction (MI) [a clinical event diagnosed as MI confirmed by hospital records], cardiac failure (symptoms or signs on medical examination or medication for heart failure in use), poorly controlled hypertension (systolic blood pressure ≥160 mmHg or diastolic ≥95 mmHg with or without medication), smoking (at the time of the interview daily smoking of any kind of tobacco), acetylsalicylic acid in use (taken regularly within the last 2 months before the interview), normal memory (Minimental State Examination score ≥24), DM and IGT.

Statistical analysis

Differences between expected and observed proportions were assessed by means of chi-square tests. Hazard ratios for the risk of stroke during the follow-up were analysed by Cox proportional hazards model with all factors included in the model. Log-rank test was used to compare the Kaplan–Meyer survival curves for development of stroke during the 12-year-long follow-up in different groups. All statistical procedures were performed using the SAS statistical software [17].

Results

A total of 1,032 patients (47.9% male) were followed up to 12 years for stroke development, mean follow-up time being 9.6 ±3.3 years. One hundred and sixty-three patients (15.8%, 95% CI ±2.2%) had DM and 127 (12.3%, 95% CI ±2.0%) of the patients had IGT. During the 12-year follow-up, ischaemic stroke occurred in 119 (11.5%) patients. Those who experienced stroke more often had history of a previous stroke or TIA than those remaining free of stroke (Table 1). Also, stroke patients were more often diabetic (32 versus 14%, $P < 0.001$), were hypertensive (48% versus 32%, $P = 0.005$), had a history of MI (17 versus 8%, $P = 0.001$), angina pectoris (35 versus 23%, $P = 0.012$) or cardiac failure (18 versus 10%, $P = 0.009$) or less frequently estimated their own health good or normal (69 versus 88%, $P < 0.001$). There was no difference regarding the presence of IGT among patients with and without stroke.

Logistic regression models were used to determine the independent risk factors for stroke development. Previous stroke (OR 4.8, 95% CI 2.9–7.8), previous TIA (OR 2.0, 95% CI 1.1–3.4), diabetes (2.4, 95% CI 1.6–3.6) and atrial fibrillation (OR 2.3, 95% CI 1.1–4.8) were significant risk factors

Table 1. Patient characteristics among 1,032 patients aged 70 years with and without subsequent stroke during the 12-year follow-up

	Stroke (n = 119) (%)	No stroke (n = 913) (%)	P-value
Male	50.4	47.5	0.55
Previous stroke	19.3	3.3	<0.0001
History of TIA	12.6	5.4	0.0021
Glucose tolerance[a]			
Normal	54.6	74.2	
IGT	13.5	12.1	
DM	31.9	13.7	<0.0001
Perceived health good or normal	69.0	88.1	<0.0001
History of hypertension[b]	51.8	31.8	<0.0001
Blood pressure categories			
Systolic			
<140 mmHg	28.6	36.4	
140–159 mmHg	21.9	18.5	
≥160 mmHg	49.6	45.1	0.090
Diastolic			
<85 mmHg	42.6	43.8	
85–99 mmHg	47.1	46.0	
≥100 mmHg	10.1	10.2	0.82
Angina pectoris	35.2	22.5	0.012
Previous MI	16.8	7.8	0.0011
Cardiac failure	18.5	10.4	0.0089
Atrial fibrillation	6.7	3.4	0.073
Claudication	18.3	12.1	0.12
Acetysalisylic acid in use	25.4	15.8	0.031
Smoking	13.5	11.0	0.42
Memory normal[c]	77.8	71.2	0.20

[a]Normal defined as fasting plasma glucose level <7.0; IGT defined 2 h after administration of 75 g of an oral glucose load plasma glucose level of between 7.80 and 11.09 mmol/l; DM defined as the current use of insulin or an oral hypoglycaemic medication, a fasting plasma glucose level of ≥7 mmol/l, or a plasma glucose level of ≥11.1 mmol/l 2 h after administration of an oral glucose load.

[b]Diagnosis in previous medical records or antihypertensive medication in use or systolic blood pressure >160 mmHg or diastolic >95 mmHg.

[c]Minimental State Examination score ≥24/30.

for stroke. Among subjects free of previous stroke or TIA, diabetes (OR 3.1, 95% CI 1.9–5.0) and atrial fibrillation (OR 2.3, 95% CI 1.0–5.3) were significant risk factors for stroke. IGT was not significant in either of the models (Table 2).

Stroke development occurred a little earlier in people with IGT than in people with normal glucose tolerance, but the difference was not statistically significant (Figure 1).

Discussion

In the elderly, IGT is not uncommon: the prevalence has been between 20 and 29% in previous studies [18–20]. In our study, the prevalence of IGT was lower, 12.3% (95% CI ±2.0%), but our study excluded institutionalised patients.

IGT is a risk factor for type 2 diabetes, with 20–50% of individuals developing type 2 diabetes over 10 years [21]. The prevalence of diabetes among acute stroke patients has increased over the years [22]. Also, the prevalence of undiagnosed diabetes and IGT is high among stroke patients; according to a Chinese study, the overall prevalence of undiagnosed diabetes was 33.5% and IGT was 21.0% [23]. In our study, the prevalence of DM among stroke patients was nearly the same, i.e. 31.9%, but the prevalence of IGT was lower, 13.5%. In view of the high prevalence of DM and IGT among stroke patients, screening for diabetes is recommended, especially in those with ischaemic stroke.

Stroke development occurred a little earlier in people with IGT than in people with normal glucose tolerance, but the difference was not statistically significant (Figure 1). However, the number of cases in our study was too small to show a 5% difference in stroke incidence between normal group and IGT group statistically significant. It seems that the atherosclerotic process in cerebral vessels caused by hyperglycaemia is slower in IGT than in clinical DM, which was a strong risk factor for stroke development in our study. The association between IGT and stroke may also be underestimated because of other causes of death, particularly deaths from coronary heart disease [24], which generally occur earlier in life and with a greater frequency than deaths from stroke [25] and also share some common risk factors with stroke.

There are some limitations in our study. The greatest one of them is the fact that the number studied (n = 1,032) was small, because the Turku Elderly Study was a cohort study. We also excluded institutionalised patients in our study, and thus those who participated tended to be healthier than those who were excluded. This fact may limit the generalisation of the findings only to the home-dwelling elderly people. Second, among those who were not diagnosed as diabetic patients, only one measurement each of fasting and 2-h glucose was available. This method is standard for most epidemiological studies. According to American Diabetes Association clinical practice guidelines, a diagnosis of diabetes requires a confirmation of elevated glucose measures on a subsequent day [26]. Because an elevated glucose measure was not confirmed by a second measure, we cannot be certain that any glucose classification was correct and not the result of random fluctuations in glycaemia. Third, the linkage of computerised records (i.e. Hospital Discharge and Death Registers) for epidemiological purposes are of course to be viewed with some caution. However, the feasibility of these registers for epidemiological studies on stroke in Finland is found to be fairly reliable, and a validation study has been done [27]. Fourth, we have no information on the amount of specific imaging investigations. On the basis of the FINSTROKE Study, in the year 1998, the combination of CT, MRI and autopsy approached 100% in Finland [15].

It is to be noted that the Turku Elderly Study was started in the year 1990 and the acceptable levels of blood pressure among the elderly were far higher than today, because the results of SHEP, Syst-Eur and other studies were not available then [28, 29]. In those days, hypertension was regarded as poorly controlled, if systolic was >160 mmHg or diastolic >95 mmHg. Of course, nowadays the target pressure in older people is much lower. However, there is still plenty of room for improvements in the implementation of guidelines in clinical practice.

Table 2. Risk of stroke during the 12-year follow-up according to Cox proportional hazards model analysis

	The whole cohort (n = 1,032), with all factors included in the model			Subjects free of previous stroke/TIA (n = 927)		
Risk factor	RR	95% CI	P-value	RR	95% CI	P-value
Previous stroke	4.75	2.90–7.78	<0.0001			
Previous TIA	1.95	1.12–3.38	0.018			
Diabetes mellitus	2.38	1.56–3.62	<0.0001	3.12	1.94–5.00	<0.0001
IGT	1.48	0.91–2.41	0.12	1.47	0.83–2.61	0.18
Atrial fibrillation	2.34	1.14–4.81	0.021	2.32	1.02–5.25	0.044
Previous myocardial infarction	1.48	0.90–2.44	0.12	1.36	0.71–2.59	0.35
Cardiac failure	1.30	0.79–2.13	0.30	1.29	0.73–2.27	0.38
Hypertension[a]	1.21	0.83–1.78	0.32	1.19	0.77–1.83	0.44
Smoking	1.53	0.91–2.58	0.11	1.75	0.97–3.17	0.065
Male sex	0.95	0.67–1.35	0.78	1.07	0.72–1.59	0.76

[a]Diagnosis in previous medical records or antihypertensive medication in use or systolic blood pressure ≥160 mmHg or diastolic ≥95 mmHg.

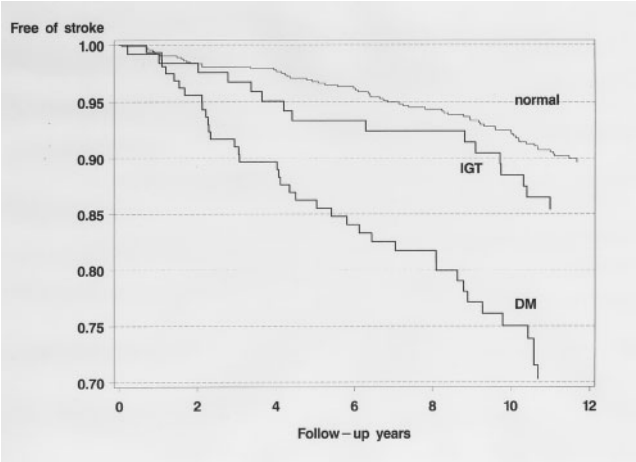

Figure 1. The probability of not having an ischaemic stroke during the 12 years of follow-up in the Turku Elderly Study among patients with normal, impaired (log-rank test P = n.s. compared with normal group) and diabetic glucose tolerance (log-rank test $P < 0.001$ compared with normal group).

From a public health perspective, identification of individuals with elevated glucose levels may provide an opportunity for intervention. However, effective screening for IGT by oral glucose tolerance test in elderly people is a rather laborious method. According to our study, in view of stroke prevention in the elderly, IGT has no predictive value beyond knowledge of standard CVD risk factors. However, if IGT patients are identified, they should be advised about modifying their lifestyle in view of preventing DM and screened and treated for other cardiovascular risk factors.

Is IGT assuming a more predominant role in stroke occurrence? Population trends in risk factors for stroke show significant improvements in hypertension detection, treatment and control, declines in the levels of cholesterol and the prevalence of cigarette smoking [30]. It is plausible, therefore, that the proportion of strokes attributable to IGT may be increasing, given the increase in the prevalence of diabetes and IGT in general population. Future studies to clear the relationship between IGT and stroke in elderly people are needed.

Key points

- Stroke tended to happen more often in the IGT group than in the normal group, but the difference was not statistically significant.
- Risk factors for stroke in elderly people are previous TIA or stroke and DM.

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Conflict of interest

None.

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