Does impaired glucose tolerance predict hypertension?

A prospective analysis

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Summary

This study evaluates prospectively the relationship between impaired glucose tolerance (IGT) and blood pressure. From a population of 1376 men and women aged 40–59 years, all those with IGT (n = 54) plus 133 age- weight- and sex-matched normoglycaemic control subjects were selected after excluding treated hypertensive patients. Blood pressure, fasting and postload blood glucose and plasma insulin were measured. At 11.5 years after the first visit 76% of the IGT patients and 80% of the control subjects were re-examined. At baseline blood pressure was significantly higher in IGT patients than in control subjects (systolic 135.5 ± 2.3 vs 127.9 ± 1.4 mmHg, p < 0.001; and diastolic 88.0 ± 1.5 vs 84.7 ± 0.7 mmHg, p < 0.05) independent of age, gender, weight, antihypertensive medication and insulin-resistance. Accordingly, hypertension was more frequent in subjects with IGT (odds ratio 2.1, 95% confidence interval (CI) 0.9–4.9). Postload insulin was significantly associated with hypertension – both at univariate and multivariate analysis – in normoglycaemic subjects, but not in those with IGT. At follow-up systolic blood pressure increased in both groups; the increase was smaller in patients with IGT (6.0 ± 2.4 vs 12.3 ± 1.6 mmHg, p < 0.05). Likewise, the 11.5 years’ cumulative incidence of hypertension was not significantly different in subjects with baseline IGT or normoglycaemia; if anything it was lower in the IGT group (odds ratio 0.36, 95% CI 0.1–1.2). In multivariate analysis incidence of hypertension was associated positively with baseline blood pressure (p < 0.0003) and negatively with IGT status (p < 0.03), while no significant association was found with insulin. In conclusion, the findings of this study question IGT as a risk factor for hypertension. Furthermore, these data do not indicate a major role for hyperglycaemia and hyperinsulinaemia per se in the aetiology of hypertension and suggest that IGT and hypertension share one or more pathogenetic factor(s) (i.e., insulin resistance, hyperactivity of the sympathetic nervous system, etc.), which induce deterioration of blood pressure control first, and hyperglycaemia later. [Diabetologia (1996) 39: 70–76]

Key words Glucose tolerance, hypertension, insulin, incidence study.

An association between hypertension and abnormalities of blood glucose metabolism, (i.e. non-insulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance (IGT)), has long been recognised. However the biological bases of this association are ill-defined [1–5]. Several hypotheses have been suggested: hypertension occurs in diabetic patients as a feature of early stages of diabetic nephropathy; diabetes or IGT develop in hypertensive patients as a result of antihypertensive medication; impairment of blood glucose homeostasis and high blood pressure are both related to a number of factors (i.e. obesity, unfavourable body fat distribution, hyperinsulinaemia, insulin resistance), which might play a role in the aetiology of both conditions [6–13]. Although several authors have proposed hyperinsulinaemia as the link be-
between hyperglycaemia and hypertension [9, 10, 12, 13], a causative role for hyperinsulinaemia in the development of hypertension has not been proved. Also, there are data which suggest that hyperglycaemia per se might induce hypertension [14]. Since no definitive evidence supporting either of these hypotheses has been provided, the mechanisms of the association between hyperglycaemia and hypertension remain a matter of debate [15-17]. Earlier studies often dealt with clinically manifest conditions (i.e. diabetes and hypertension) and were therefore unable to completely eliminate the effect of major confounders such as obesity, early diabetic nephropathy and the diabetogenic effect of some medications. Furthermore as almost all the previous studies were cross-sectional in design they did not allow evaluation of any cause-effect relation or establishment of the time sequence of events leading to the development of abnormal glucose tolerance and hypertension.

In an attempt to elucidate further the mechanisms of the association between IGT and hypertension, we investigated prospectively a cohort of individuals with IGT together with a group of normoglycaemic control subjects.

Subjects and methods

Between 1979 and 1980, 1376 telephone company employees, male and female (age range 40-59 years), underwent an oral glucose tolerance test (OGTT) as part of a company-sponsored health screening programme. All those with IGT (n = 54) according to World Health Organization (WHO) criteria [18] and 133 normoglycaemic control subjects, matched for age (+ 5 years), sex and body mass index (BMI) (+ 1 kg/m²), were selected to participate in this study. Exclusion criteria were current or previous use of antihypertensive or hypoglycaemic drugs. No subject was taking other drugs known to affect glucose tolerance. All participants were free of symptomatic coronary heart disease as assessed by the WHO questionnaire on angina and myocardial infarction.

The OGTT was performed in the fasting state under previously described conditions [18]; blood was drawn immediately before and 2 h after a 75-g oral glucose load for glucose and insulin determination. Glucose was measured by the glucose oxidase method in venous whole blood immediately deproteinized with perchloric acid [19]. Serum insulin was measured by radioimmunoassay [20]; within-day and between-day coefficients of variation in our laboratory were 5 and 7 %. Serum creatinine and creatinine clearance were measured for all participants on a timed urine collection [21]. Blood pressure was measured in the supine position on the right arm after a 5-min rest; a standard sphygmomanometer of appropriate cuff size was used and the first and fifth phases were recorded. Values used in the analysis are the average of three readings taken at 2-min intervals.

The follow-up visit took place in 1991-1992, 11.5 years after the first examination. Of the original cohort 79 % was traced and examined. Measurements were performed according to the same protocol as at baseline. On both occasions the glucose tolerance status of the participants was unknown to observers.

The baseline definition for hypertension was blood pressure greater than or equal to 160/95 mm Hg; subjects on antihypertensive drugs were excluded from the study at this stage. Since some subjects had been treated with antihypertensive medication between the baseline and follow-up examinations, hypertension at follow-up was defined as blood pressure greater than or equal to 160/95 mm Hg or antihypertensive treatment [22]. For prospective blood pressure analysis hypertensive subjects at baseline were excluded from the study (9 in the IGT group and 15 in the normoglycaemic group).

Details concerning the study protocol and the recruitment procedures have been previously published [23].

Statistical analysis

Results are given as percentage or mean ± SEM. Unpaired t-test and two-way analysis of variance were used to compare group means; for very skewed variables (i.e., plasma insulin) significance tests were performed after log transformation – row values are given in the tables. Differences between proportions were tested by the chi square test. Multivariate regression analyses were also performed to evaluate the independent association between measured variables. All analyses were performed by the computer program SPSS [24].