Cardiac risk profile in diabetes mellitus and impaired fasting glucose

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Abstract

Objective
Mortality of diabetic patients is higher than that of the population at large, and mainly results from cardiovascular diseases. The purpose of the study was to identify the prevalence of cardiovascular risk factors in subjects with diabetes mellitus (DM) or abnormal fasting glucose (FG) in order to guide health actions.
Methods
A population-based cross-sectional study was carried out in a representative random cluster sampling of 1,066 adult urban population (=20 years) in the state of Rio Grande do Sul between 1999 and 2000. A structured questionnaire on coronary risk factors was applied and sociodemographic characteristics of all adults older than 20 years living in the same dwelling were collected. Subjects were clinically evaluated and blood samples were obtained for measuring total cholesterol and fasting glycemia. Statistical analysis was performed using Stata 7 and a 5% significance level was set. Categorical variables were compared by Pearson's chi-square and continuous variables were compared using Student's t-test or Anova and multivariate analysis, all controlled for the cluster effect.
Results
Of 992 subjects, 12.4% were diabetic and 7.4% had impaired fasting glucose. Among the risk factors evaluated, subjects who presented any kind of glucose homeostasis abnormality were at a higher prevalence of obesity (17.8, 29.2 and 35.3% in healthy subjects, impaired fasting glucose and DM respectively, $p<0.001$), hypertension (30.1, 56.3 and 50.5% in healthy subjects, impaired fasting glucose and DM, respectively, $p<0.001$), and hypercholesterolemia (23.2, 35.1 and 39.5 in healthy subjects, impaired fasting glucose and DM respectively, $p=0.01$).
Conclusion
Subjects with any kind of glucose homeostasis abnormality represent a group, which preventive individual and population health policies should target since they have higher prevalence of coronary artery disease risk factors.

INTRODUCTION

Heart disease is accountable for up to 80% of mortality in type 2 diabetes mellitus (DM) patients. In fact, the relative risk of death from heart events adjusted to age group is three times higher in diabetics than that of the population in general.[21] A recent observational study shows that the risk of death from coronary heart disease in type 2 DM patients is similar to that for non-diabetics who have suffered a prior acute myocardial infarction.[8] Women are generally at a lower risk for heart disease than men, however for diabetic women this is not so.[9]

The reasons for accelerated evidence of arteriosclero-

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sis in diabetic patients remain largely unknown, however the putative mechanisms underlying accelerated arteriosclerosis have been suggested to be the direct toxic effects of glucose on vasculature, insulin resistance, and the association of DM with other risk factors.[8]

It is widely known that type 2 DM is associated to a number of cardiovascular risk factors, including systemic arterial hypertension (SAH), obesity, insulin resistance, microalbuminuria, lipid and plasma lipoprotein abnormalities, in general, high triglyceride levels and decrease in high density lipoprotein cholesterol (HDL cholesterol). The association of these risk factors has been called metabolic syndrome or X syndrome.[17] The relationship between hyperglycemia and cardiovascular disease can be attributed to the high prevalence of these risk factors in metabolic syndrome patients or to a common precursor of all these factors.

The Multiple Risk Factor Intervention Trial (MRFIT) clearly confirmed that SAH, hypercholesterolemia and smoking are independent predictive factors of mortality among patients with cardiovascular disease, and the presence of at least one of these risk factors has a greater impact on the mortality among diabetic patients than of that among non-diabetics.[21] More recently, UK Prospective Diabetes Study (UKPDS) results obtained in a comprehensive multi-centered study carried out in the UK have confirmed the greater effect of the classical coronary heart disease risk factors in diabetic patients.[25]

A type 2 DM epidemic has been taking place in the last few years and tends to spread in the next decade.[14,15] Therefore, type 2 DM complications, among which cardiovascular complications emerging as one of the greatest threats to health worldwide, represent huge social and economic costs.[4] A recent study proved that changes in patient lifestyle (exercising regularly and weight reduction) can decrease the incidence of type 2 DM in glucose intolerant patients.[2,24]

Therefore, identifying the global risk profile of the population suffering from DM and from other glucose homeostasis abnormalities is essential to develop health policies. The present study aims at identifying the true prevalence of risk factors for coronary heart disease in individuals showing different glucose homeostasis abnormalities.

METHODS

This is population-based analytical observational cross-sectional study carried out in the state of Rio Grande do Sul (RS). A database built for the original study was used to assess the prevalence of risk factors for coronary heart disease in RS.[7] The sample was composed of 1,066 subjects drawn from a cluster random sampling according to the following parameters: 1) population size: infinite; 2) error (absolute accuracy): 3%; 3) expected prevalence: 50% (maximum variability); 4) confidence level: 95%. To ensure the study would be representative of the urban population in RS, the sample was calculated according to the population of the municipality where each one of the 19 coordination offices of the State Health Department were based, thus accounting for the 19 micro-regions in the state.

The present study was conducted between July 1999 and October 2000. A structured questionnaire on risk factors (lack of physical activity, diabetes, smoking, SAH, hypercholesterolemia) and sociodemographic characteristics was applied to the adult population over 20 years of age in the selected area. Interviewers, nursing technical staff, and medical students were trained according to the Joint National Committee[19] (1997) standards to ensure correct blood pressure readings and adequate questionnaire completion. Weight, height, and blood pressure measurements were recorded by the interviewers. To determine fasting glucose and total blood cholesterol values interviewers asked for blood samples after requiring subjects to fast eight to 12 hours prior the testing.

Blood was drawn according to standard procedures the day following the interview. Before being frozen the samples were kept in fluoride tubes inside an ice cooler. Blood pressure was measured twice during the home visit with an interval of at least three minutes between the two readings. The second reading was recorded. The scales and sphygmomanometers were Inmetro (National Institute of Metrology, Standardization and Industrial Quality) adjusted and certified. All subjects signed a consent form agreeing to the procedures.

The next step was to identify and compare risk factors. Therefore, subjects were classified into three groups by their levels of glucose homeostasis: normal (fasting glucose <110 mg/dL), impaired fasting glucose (fasting glucose =110 e <126 mg/dL) or diabetic (fasting glucose =126 mg/dL or DM history or use of anti-diabetic medication). Systemic arterial hypertension was ascertained if the subject had blood pressure of =140/90 mmHg, or lower if under anti-hypertensive medication. Hypercholesterolemia was ascertained if total blood cholesterol was =200 mg/dL. Obesity was considered present if body mass index (BMI; calculated by dividing weight in kilos by height in squared meters) was =30 kg/m^2. Subjects who did not exercise at least three times a week were considered sedentary. Current tobacco consumption, regardless of the number of cigarettes,

Table 1 - Sample features according to gender.

Features	Male	Female	p-value
Age (years)	43.0 (95% CI: 40.3-45.7)	44.8 (95% CI: 42.4-47.1)	0.02
Age ≥60 years (%)	16.2	19.5	0.08
Family income less than 6 minimum wages (%)	71.3	77.6	0.004
Schooling ≥8 years (%)	35.0	47.8	<0.001
Attended public health services in the last year (%)	46.0	59.3	<0.001
Fasting glucose (mg/dL)	98.7 (95% CI: 95.5-101.9)	96.6 (95% CI: 93.4-99.8)	0.16
Impaired fasting glucose (%)	8.9	6.1	0.07
Diabetes mellitus (%)	12.6	12.3	0.85
Total cholesterol (mg/dL)	172.11 (95% CI: 160.9-183.3)	179.3 (95% CI: 170.5-188.2)	0.005
Blood cholesterol ≥200 mg/dL(%)	22.4	29.1	0.03
SBP (mmHg)	129.1 (95% CI: 123.7-134.5)	127.0 (95% CI: 120.7-133.2)	0.07
DBP (mmHg)	82.5 (95% CI: 79.2-85.8)	80.8 (95% CI: 77.2-84.4)	0.02
SAH (%)	34.3	35.0	0.85
Lack of physical activity (%)	72.6	71.2	0.71
BMI (kg/m^2)	26.4 (95% CI: 25.9-26.8)	26.1 (95% CI: 25.5-26.7)	0.41
BMI >30 kg/m^2	19.7	21.7	0.25
Total	470	522	

SBP: systolic blood pressure; DBP: diastolic blood pressure; SAH: systemic arterial hypertension; BMI: body mass index.
In order to compare the 2 groups: Pearson's c^2 (proportions) and Student's t -test (means).

was considered smoking. Family income, number of family members, and having attended the public health service in the last 12 months were also assessed.

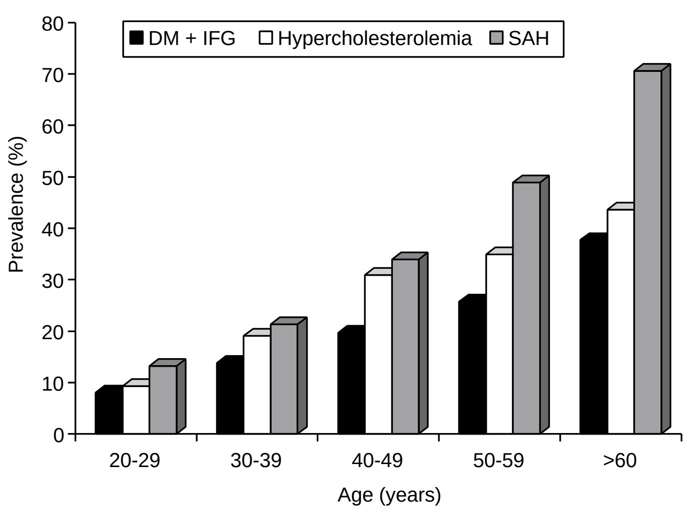
Stata 7 statistical software was used in the data analysis. Absolute and relative risk factor frequencies were calculated, in addition to their distribution according to age group. The data were expressed as means, confidence intervals or percentages. A 5% significance level was set. Categorical variables were compared using Pearson's chi-square test. Continuous variables were compared using Student's t-test or Anova. All of these statistic tests were bivariate and to control for effect of the study design (cluster sampling) it was used various "svy" Stata commands, creating clusters representing each one of the micro-regions in the state of RS. Logistic regression models, controlled for the effect of the study design, were applied to control for the effects of age and BMI on the associations found between the risk factors and the degree of glucose homeostasis abnormality. These models were used to separately compare healthy subjects to those presenting impaired fasting glucose or diabetes.

RESULTS

There were studied 1,063 out of 1,066 subjects initially selected. This represented a loss of 0.3%. Of these, there were complete data on 992 subjects, thus representing 93% of the total sample, to classify them in three different groups according to the level of glucose homeostasis. Representativeness of the adult urban population was evidenced by comparing the demographic data of the sample to the 2000 Population Census carried out by the Brazilian Geography and Statistics Institute (Instituto Brasileiro de Geografia e Estatística, IBGE).

The average age of the sample was 44 years (95%CI: 41.3–46.5), with 18% of the sample being over the age of 60, 47.4% were male. Approximately 74% had family income equal to or less than six minimum wages, while 42% had a family income equal to or less than three minimum wages. About 42% of the sample did not finish elementary and junior high school education (less than eight years of schooling). Table 1 shows the main features according to gender. There were statistically significant differences in schooling and family income (both lower in women) when related to having attended the public health service in the last year (greater for women) and to the presence of higher levels of total cholesterol and women in the older age group.

Diabetic prevalence was 12.4% (N=123), while 7.4% (N=74) presented impaired fasting glucose. In the diabetic group, 31.7% (N=39) were not aware of their disease. The figure shows the direct association between



In order to compare age group to the 3 variables: p<0.05 (Pearson's correlation)

Figure - Evalence of glucose homeostasis abnormality, SAH, and hypercholesterolemia according to age group.

Table 2 - Risk factor prevalence according to the different levels of glucose homeostasis.

Features	Healthy	IFG	DM	p -value
Age (years)	42.0 (95% CI: 38.9-45.0)	49.1 (95% CI: 45.8-52.4)	53.4 (95% CI: 50.8-56.0)	<0.001
>60 years	14.0	25.7	39.0	<0.001
Men (%)	46.4	56.8	48.0	0.14
Smoking (%)	32.4	39.2	30.9	0.30
Obesity (%)	17.8	29.2	35.3	<0.001
SAH (%)	30.1	56.3	50.5	<0.001
Cholesterol (mg/dl)	172.7 (95% CI: 160.9-184.5)	183.4 (95% CI: 173.2-193.6)	193.5 (95% CI: 185.9-201.2)	<0.001
Hypercholesterolemia (%)	23.2	35.1	39.5	0.01
Lack of physical activity (%)	70.7	76.1	77.2	0.12
Family income less than 6 minimum wages (%)	73.6	80.8	77.0	0.18
BMI (kg/m^2)	25.8 (95% CI: 25.4-26.2)	27.6 (95% CI: 26.7-28.4)	28.3 (95% CI: 27.5-29.0)	< 0.001
Attended public health services in the last year (%)	51.1	57.1	63.4	0.003
Total	795	74	123	

IFG: Impaired fasting glucose; DM: diabetes mellitus; SAH: systemic arterial hypertension; BMI: body mass index.
In order to compare the 3 groups: Pearson's c^2 (proportions) and ANOVA (means).

older age and higher DM prevalence and impaired fasting glucose, as well as hypercholesterolemia, and systemic arterial hypertension.

Table 2 compares risk factors for coronary heart disease among diabetics, subjects with impaired fasting glucose and healthy subjects. When comparing the three groups, subjects with impaired fasting glucose and diabetes presented a statistically significant association to older age, BMI index, in addition to obesity, SAH, and hypercholesterolemia. The post hoc analysis showed that subjects with impaired fasting glucose were older, had a higher prevalence of SAH, hypercholesterolemia, and obesity. Both the group of subjects with impaired fasting glucose and the diabetic group had sought the public health service significantly more often.

Gender, family income, schooling, hypercholesterolemia, hypertension, lack of physical activity, and obesity were not different among subjects who were not aware of being diabetic from those who had already been diagnosed as such. However, the latter showed a lower fasting glucose than the former (137.8 mg/dL *vs* 182.7 mg/dL, p=0.004). They also had a lower prevalence of smoking (26.2% *vs* 41%, p=0.04). These data are shown in Table 3.

In order to control for the effect of age and BMI on SAH prevalence and blood cholesterol levels among healthy subjects and those with impaired fasting glucose, odds ratios were calculated by using logistic regression models. There is an association between SAH (OR=1.93, 95% CI=1.07-3.48) and impaired fasting glucose, regardless of age and BMI, but there is no association to blood cholesterol levels (OR=1.16, 95% CI=0.74-1.83). While comparing healthy to diabetic subjects, also by logistic regression analysis, it was not observed an independent association of age and BMI between SAH (OR=0.97, 95% CI=0.61-1.53) and high cholesterol (OR=1.49, 95% CI=0.94-2.37) and diabetes.

DISCUSSION

The prevalence of diabetes found in this sample was greater than that found by Malerbi et al[12] in Porto Alegre in 1992 (8.9%). Data in the present study were based on

Table 3 - Prevalence of coronary heart disease risk factors according to the blood glucose in the diabetic adult urban population in RS between 1999 and 2000.

Features	Subjects who were not aware of being diabetic	Subjects who were aware of being diabetic	p-value
Age (years)	50.6 (95% CI: 46.6-54.6)	54.7 (95% CI: 52.3-57.2)	0.04
Men (%)	46.2	48.8	0.74
Family income less than 6 minimum wages (%)	78.9	76.2	0.61
Schooling <8 years (%)	39.5	45.2	0.49
Fasting blood glucose	182.7 (95% CI: 163.7-201.6)	137.8 (95% CI: 113.2-162.2)	0.004
Smoking (%)	41.0	26.2	0.04
SAH (%)	35.3	57.3	0.16
Cholesterol (mg/dl)	182.2 (95% CI:169.6-194.8)	199.4 (95% CI:187.8-211.0)	0.08
Hypercholesterolemia (%)	33.3	42.7	0.26
Lack of physical activity (%)	71.8	79.8	0.37
BMI (kg/m^2)	28.9 (95% CI: 26.9-30.9)	27.9 (95% CI: 27.0-28.8)	0.37
Obesity	41.0	32.5	0.39
Attended public health services in the last year (%)	64.1	63.1	0.88
Total	39	84	

SAH: systemic hypertension; BMI: body mass index.
In order to compare the two groups: Pearson's c^2 (proportions) and Student's t-test (means).

new diagnosis criteria having lower fasting glucose cut-offs than the one adopted in the study mentioned above (126 mg/dL *vs* 140 mg/dL). However, the great majority of patients diagnosed as diabetics in Malerbi et al. study were considered so because glycemia was greater than 200 mg/dL after oral glucose tolerance test (75 g). It is known that this criterion is equivalent, in regard to the prevalence of diagnosed diabetes, to the one using fasting glycemia greater than 126 mg/dL. Both studies considered the patients who, despite presenting fasting glycemia levels lower than the above-mentioned levels, reported a previous history of diabetes and anti-diabetic medication use. It should be taking into consideration, though, that the current study encompassed a sample of the whole adult urban population in RS, while the previous only included a sample of the city of Porto Alegre. This increase in the prevalence of diabetes can be compared to what has been taking place in developed and developing countries.[14,16,22]

It is likely that this increase in the prevalence of diabetes is a consequence of the established prevalence of obesity in Brazil according to three comprehensive cross-sectional studies carried out between 1975 and 1997.[15] High obesity in the target population in both sexes reinforces this hypothesis. In addition, it was observed a higher BMI and a higher obesity rate among subjects with some degree of glucose homeostasis abnormality (diabetes or impaired fasting glucose).

High obesity rates were observed in the state of RS (19.5 and 21.8% in men and women respectively) than in Brazil as a whole (6.9 and 12.5% in men and women respectively).[15] Despite the higher prevalence of diabetes in RS when compared to the 1992 study, this higher prevalence is still lower than expected because of the high number of obese subjects. Other determining factors for impairment of glucose homeostasis besides obesity (diabetes genetic predisposition, insulin resistance) are not likely to been so frequent. The low prevalence of type 2 diabetes in relation to the high prevalence of obesity has been recently reported in a rural population in Chile.[18] In other regions of Brazil, in a specific subpopulation,[3] the increase in the incidence of diabetes was parallel to the increase in obesity, thus regional differences in factors determining diabetes, besides obesity, are operating factors.

Impairments of glucose homeostasis still not considered to be diagnostic of diabetes were observed in 7.4% of the subjects in this study, which is lower than the proportion found in Porto Alegre in 1992 (12.2%).[12] Data of the present study are based on the recommendations of the American Diabetes Association,[6] which introduces the impaired fasting glucose category (fasting glycemia between 110 mg/dL and 126 mg/dL). The previous data were based on glucose tolerance test results. The impaired fasting glucose category is suggested to be equivalent to the glucose intolerance, but this has not been evidenced. Subjects with high risk of cardiovascular disease would be better identified by glucose tolerance tests since 30% of subjects with high blood glucose after being subject to this test present fasting glycemia lower than 100 mg/dL.[1] Subjects with impaired fasting glucose present lower cardiovascular mortality than those with diabetes or glucose intolerance.[23] Despite the controversy in regard to diagnosing diabetes,[1,6] fasting glycemia testing is more economic and easier to perform, thus being preferred in studies with a great number of subjects, such as this one.

It was seen a lower number of diabetic subjects who were not aware of their condition before the study: 46% in the Brazilian Diabetes Census[12] compared to 31.7% in the present study. These proportions indicate that measures taken by the Brazilian Ministry of Health[13] aiming at diagnosing diabetes have been effective, at least in RS. Considering the high costs of treating the chronic complications of diabetes, which tend to occur in up to 50% of type 2 diabetics at the time of diagnosis,[26] it is essential that effective measures well-known to prevent diabetes (weight reduction and physical exercises)[2,24] be put in practice after an early diagnosis through glucose homeostasis evaluation. The new strategies recently proposed by the Brazilian Ministry of Health are very important in this context.[13]

The increase in the number of subjects with some kind of glucose homeostasis abnormality compared to age increase reinforces previous information on glucose tolerance decreasing as people age. These data are shown in this study both by the higher average age in the impaired fasting glucose group as well as in the diabetic group, in addition to the higher percentage of subjects over 60 years of age in these groups. The same can be said on the greater number of subjects with hypertension and hypercholesterolemia in the older age groups, according to previous data from other populations.[10]

The smaller number of smokers among diabetic subjects was already expected, seeing that they are a subgroup that knowingly attends health services more than non-diabetic subjects. Thus, the former are targeted by measures aimed at preventing the chronic complications of diabetes, including quitting smoking.[11,20]

Characteristically, type 2 diabetics present higher triglyceride levels and lower HDL cholesterol without, however, they do not present higher levels of low-density lipoprotein cholesterol (LDL cholesterol) than expected for the general population.[17] Data of the present study showed higher total cholesterol for diabetic subjects, but this association was not confirmed when controlled for BMI and age. However, even though it can not be determined a causal relation between diabetes or impaired fasting glucose and increase in total cholesterol, the association of these variables, and particularly that both depended on subjects' overweight, is extremely relevant to the goals to be attained in caring for this population. These goals should be mainly based on preventing obesity through educational measures.

Subjects with some degree of glucose homeostasis abnormality presented a higher SAH prevalence, which was no longer seen when the multivariate analysis was performed, controlling for the effects of age and BMI. However, the association of higher SAH prevalence remained unchanged in the impaired fasting glucose group. Considering the rich literature data concerning the association of diabetes to SAH,[5,10] the differences in the study data can be attributed to the greater concern diabetics have with their health and, therefore, there is a greater chance their pressure levels are under control. This hypothesis is strengthened by the higher number of diabetic patients attending the public health system in the last year (63.4%) compared to non-diabetics (51.1%) and those with impaired fasting glucose (57.1%). As previously mentioned, there is no support for a causal relation between diabetes and SAH, but their association is fact, just as these variables depend on the presence of overweight. Therefore, the same measures taken to prevent obesity shall impact on a lower number of hypertension subjects.

The present study on the prevalence of risk factors in a subpopulation of subjects with high risk for coronary disease (glucose homeostasis abnormalities) highlights the importance of diagnosing and, at a second stage, monitoring the subjects for complications frequently seen. Identifying these subjects as a target group is essential to establishing preventive measures at the individual and population level. At an earlier stage still, the ideal intervention for preventing diabetes, hypertension and dyslipidemia can be carried out partially by health programs which target high risk populations (particularly subjects with overweigh and obesity) by encouraging physical activities and weight reduction.

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