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High prevalence of prediabetic states in Primary Care in Spain: the Desire study

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ABSTRACT. Aim: To assess the prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in the population older than 45 years assigned to Primary Care in Spain, and to evaluate whether the combination of both level of fasting glucose and central obesity could be useful to identify people with diabetes, IFG, IGT and insulin resistance (IR). Methods: An observational, multicentre, cross-sectional study including 4231 subjects. According to the presence of a fasting glucose equal to or higher than 90 mg/dl and waist circumference ≥94/80 cm (men/women) or known type 2 diabetes (T2DM), subjects were divided in two groups: study and control groups. Study group subjects and a subset of the control group were referred to hospital for classification according to presence of T2DM, HOMA-IR, fasting plasma glucose and oral glucose tolerance test results. Results: Prevalence of known T2DM: 11.3% [95% CI 10.5-12.1]. Prevalence of unknown T2DM, impaired glucose tolerance, impaired fasting glucose and insulin resistance (IR): 5.4% [4.1-7.8], 13.5% [10.7-17.1], 3.9% [2.7-6.2] and 17.9% [14.5-22.1] respectively. The sensitivity of the screening test for any glucose metabolism alteration was 86.5%. Conclusions: We have found that in Spain the prevalence of IFG and IGT in population older than 45 years assigned to Primary Care is high, and similar to the French population. This prevalence predicts higher rates of diabetes prevalence than WHO's estimation. The combination of fasting glucose and waist circumference measurement could be an easy to use tool to identify those subjects at risk of having diabetes, IFG, IGT and IR.
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Key words: Impaired glucose tolerance, impaired fasting glucose, insulin resistance, type 2 diabetes mellitus.

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INTRODUCTION

Type 2 diabetes (T2DM) is an important risk factor for the development of cardiovascular disease (1, 2) (CVD), which is still the most important cause of mortality in Western societies. The increasing prevalence of T2DM (3), the difficulty to maintain glucose control (4) and the availability of interventions that have been demonstrated to decrease the development of the disease, highlight the importance of its early identification and prevention.

T2DM is usually preceded by a period of minor hyperglycemia, known as prediabetes, which is associated with an increase in the hazard ratio for CVD (5). Depending on whether the fasting glucose (FG) or the two-hour glucose post-oral glucose tolerance test (2hG- OGTT) is used, two categories of prediabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) can be identified. Even though FG and 2hOGTT are different tests, there is a relationship between them, in fact, in the Hoorn study 95% of the IGT population had a fasting glucose level equal to or more than 90 mg/dl (6).

Epidemiological studies have shown that the prevalence of IFG and IGT varies considerably among different ethnic groups (7). In Spain, studies on the prevalence of prediabetic states have been limited to specific areas (8-14), with no data available from the Spanish population as a whole. Furthermore, a simple method, based on a Spanish population, would be very useful to identify persons with prediabetes and insulin resistance (IR), which, in concert with progressive β-cell failure, produces hyperglycemia that in turn is associated with the development of cardiovascular complications.

The primary objective of the present study is to estimate the prevalence and the incidence of prediabetic states (IFG and IGT) in the population older than 45 years

assigned to Primary Care centres in Spain, and secondly to evaluate whether the combination of both level of fasting plasma glucose equal to or higher than 90 mg/dl and the International Diabetes Federation (IDF) definition for central obesity could be useful to identify people with diabetes, IFG, IGT and IR. In this study we will show the data of the cross-sectional study.

PATIENTS AND METHODS

Design

Investigators from hospitals distributed all across Spain participated in the study. Each hospital contacted several Primary Care centres. The screening phase was undertaken by the Primary Care investigator and classification phase by the Hospital investigator. Each investigator was provided with a list of random numbers obtained from the list of subjects ≥45 years assigned to his/her Primary Care centres.

Subjects were included in the study, if none of the following exclusion criteria was met: type 1 diabetes, pregnancy, subjects with only temporally assignment to the Primary Care investigator, T2DM patients being treated with insulin, and subjects that, according to the investigator criteria, were at a significant risk of not completing the study. Subjects who have T2DM or the combination of both FG ≥90 mg/dl and IDF central obesity definition (waist circumference ≥94 cm for men and ≥80 cm for women) were identified by the Primary Care investigator as a study group and referred to the hospital. A randomly selected subgroup of subjects without these criteria was also referred in order to have a control group. This group was needed to estimate the prevalence of IFG, IGT and IR because, per protocol, insulinemia and OGTT were only performed in the population referred to the Hospital investigator.

At the hospital, subjects were classified in six groups according to the HOMA-IR, fasting plasma glucose (FPG) and results from a standard OGTT: (a) known T2DM, when patients reported a history of diabetes diagnosed by a physician; (b) *de novo* T2DM, when according to WHO criteria (15) the patients showed a FPG ≥126 mg/dl or a 2-hour glucose level ≥200 mg/dl in the OGTT; (c) IGT, when FPG was <126 mg/dl and the 2-hour plasma glucose level was ≥140 and <200 mg/dl; (d) IFG, when FPG was ≥110 and <126 mg/dl; (e) isolated IR, when the HOMA-IR was above the 75th percentile of the HOMA value of the control group with none of the above alterations being present; (f) normal glucose metabolism, when no previous category could be applied. When more than one glucose metabolism alteration was present, patients were classified in the most severe category, using the following range from least to most severe: IR, IFG, IGT, new T2DM, and known T2DM.

The quantification of IR was made by the HOMA-IR method (16). It was calculated according to the following formula: HOMA = [Insulin (μU/ml) x Glycaemia (mmol/l)]/22.5. Cut-off point for IR assessed by HOMA-IR was calculated as the 75th percentile of the control group population (17). Hyperinsulinemia was defined as a value greater than the 75th percentile of the control group.

Sample size calculation

Sample size was calculated to assess the prevalence of prediabetic states (IFG and IGT) in the population older than 45 years assigned to Primary Care centres in Spain. The sample size needed, for a 95% confidence interval (CI) of ±2% (for the wider interval p=0.5), was 2400 patients. Assuming 50% of patients in Primary Care centres were without inclusion criteria, the sample was increased to 4800 screened patients in Primary care Centres.

Ethical aspects

The study was performed according to the recommendations of the Spanish Society of Epidemiology (18) and the Council for International Organizations of Medical Sciences (19). The study was approved by the Research Ethics Committee of Hospital General Universitario de Valencia. Subjects gave their written informed consent before entering the study.

Statistical analysis

Point prevalence estimates and their 95% CI were used to measure disease frequency. The overall age and sex-

Table 1 - Participating patients by Spanish Autonomous Community.

Autonomous Community	Patients
Andalusia	406
Aragon	178
Asturias y Cantabria	130
Balearic Islands	24
Canary Islands	135
Castilla & León	161
Castilla La Mancha	390
Catalonia	282
Valencia	718
Extremadura	210
Galicia	274
Madrid	488
Murcia	161
Navarra	87
Basque Country	567
Total (number)	**4231**

Table 2 - Characteristics of the study, control group and total population.

	Study group	Control Group	p	Total population
Demography	n=2354	n=1877		n=4231
Age (years)	62±9.8	60.3±11	<0.0001	61.2±10.4
Males (%)	44.6%	44%	ns	44.4%
Caucasians (%)	99.4%	99.6%	ns	99.5%
Smokers (%)	17%	22.5%	<0.0001	19.3%
Medical history				
Previous coronary	7.7%	4%	<0.0001	6.1%
Previous stroke	3.3%	2.1%	0.020	2.7%
Previous PVD	5.6%	4.6%	ns	5.2%
Familiar history of T2DM	36.9%	21.9%	<0.0001	30.2%
Hypercholesterolemia	34.9%	24.9%	<0.0001	30.6%
Hypertrygliceridemia	11.2%	4.1%	<0.0001	8.1%
Hypertension	44.5%	27.1%	<0.0001	38.5%
Biochemical parameters				
Glucose (mg/dl)	128±34	96±14	<0.0001	114±32
Physical examination				
dBP (mmHg)	81.2±10.2	78±9.8	<0.0001	79.75±10.1
sBP (mmHg)	137.5±17.9	130.7±17.9	<0.0001	134.4±18.2
Waist circumference (cm)	99.9±10.6	87.1±10.7	<0.0001	94.2±12.4
Hip circumference (cm)	106.7±9.7	100±9.8	<0.0001	102.7±10.6
Weight (kg)	78.2±13	67.8±12	<0.0001	73.6±13.6
Height (cm)	160.7±9.1	160.6±8.7	ns	160.7±8.9

Values are means ± SD or proportions (%); ns= non significant.
dBP= diastolic blood pressure; sBP= systolic blood pressure; PVD= peripheral vascular disease.

specific prevalences were calculated for current IR, IFG, IGT and DM, as well as the prevalence according to covariates of interest. The level of significance used in all the analyses was p<0.05. Data were analyzed with the SAS V9.1 software.

RESULTS

Selection phase and demography

Investigators from 60 hospitals and 220 Primary Care centres distributed throughout Spain participated in the study (Table 1).

Demographics and data from subjects included in the study are shown in Table 2. The flow-chart of the study is shown in Figure 1. People that refused to participate (n=972) were significantly older (64.2±12.7 years vs 61.2±10.4 years, p<0.0001), had a higher proportion of coronary heart disease (11.8% vs 6.1%, p<0.0001) and cerebrovascular disease (6.9% vs 2.7%, p<0.0001), a lower proportion of familial antecedents of T2DM (16.8% vs 30.2%, p<0.0001), known T2DM (0.7% vs 13.7%, p<0.0001) and dyslipidaemia (30.2% vs 34%, p<0.04). Proportion of males was also higher in the population that refused to participate in the study. Fasting glucose was significantly lower in this population, though the difference was not clinically relevant (102.6 vs 97.2 mg/dl, p<0.0001).

Finally, 4231 subjects (enough for the primary objective since more than 50% of the patients fulfilled criteria for the study group) agreed to take part in the study. The subjects of the study group and a control subgroup of 211 people (randomly selected from the control group) were finally referred to the hospital. The baseline characteristics of this control group, except for its younger age (58.2±9.5 years vs 60.5±11.1 years, p=0.004), were well matched with those of the rest of the control group.

Cut-off point for IR as assessed by HOMA-IR was 3.29. Corresponding figures for hyperinsulinemia were 13.05 μU/mL for men and 14.5 μU/mL for women [95% CI 10.5-12.1].

Prevalence of IFG, IGT and IR for the whole population were 13.3% (95% CI 10.6-16.9); 14.1% (11.3-17.7) and 13.9% (10.8-17.8) respectively using the new criteria from American Diabetes Association (20) for IFG. Prevalence of known and unknown T2DM were 11.3% (95% CI 10.5-12.1), 5.4% (4.1-7.8). The sensitivity, specificity, PPV, Negative Predictive Value (NPV) and diagnostic success of waist circumference and glucose level for the presence of any glucose metabolism alterations are shown in Table 3. The PPV, NPV, sensitivity and specificity of the study group for the presence of IR were 62.7%, 75%, 89.1% and 38.2% respectively.

The prevalence of new T2DM, IFG, IGT and IR (excluding already known T2DM) in study group vs control group (with IFG defined as FG ≥110 mg/dl) is shown in Table 4. If the new ADA definition for IFG had been used (20),

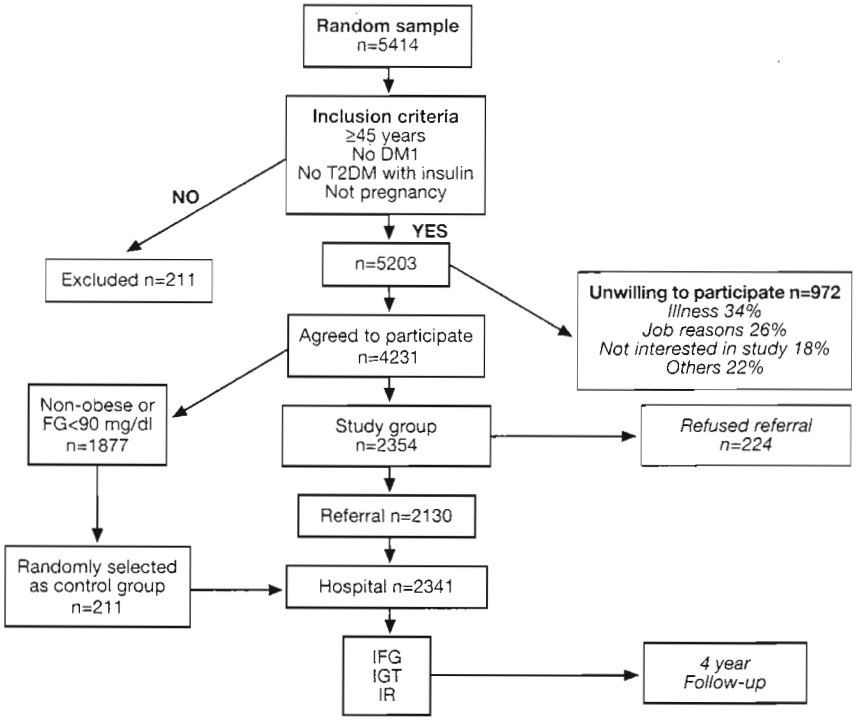

Fig. 1 - Flow-chart of the study. DM1= diabetes mellitus type 1; T2DM= diabetes mellitus type 2; DM= diabetes mellitus; FG= fasting glucose; IGT= impaired glucose tolerance; IFG= impaired fasting glucose; IR= isolated insulin resistance.

prevalence of IFG would be 16.9% and 11.9% in study group vs control group respectively. Prevalence of IR would change to 10.8% in the study group and to 16.4% in the control group. When we analyzed the prevalence of IR as a whole (including patients with other glucose metabolism abnormalities that also had IR) the figure was 56.6% (including known T2DM) and 49.5% (excluding known T2DM) in the study group, and 25% in the control group.

Table 3 - Sensitivity, specificity, positive and negative predictive values.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic success (%)
Men	84.3	43.6	80.5	50.2	73.5
Women	88.6	49.6	74.9	71.6	62.9
All	86.5	47.4	77.4	62.8	73.9

PPV= positive predictive value; NPV= negative predictive value.

Table 4 - Prevalence of glucose metabolism alterations in Study and Control Group.

	Study Group		Control Group	
	%	CI 95%	%	CI 95%
Novo T2DM	5.9	7.9-10.5	2.5	1.1-5.7
IGT	15.9	14.4-17.6	11.6	7.8-16.7
IFG	5.7	4.8-6.8	2.5	1.1-5.7
IR	16.5	15-18.2	19.1	14.2-25.1

DM= diabetes mellitus; CI= confidence Interval; IGT= impaired glucose tolerance; IFG= impaired fasting glucose; IR= isolated insulin resistance.

DISCUSSION

The present study shows that the prevalence of IFG and IGT in the adult population in Spain assigned to Primary Care centres, where more patients are present and managed, is high. As much as 27.4% of the Spanish adult population is in a prediabetic state; furthermore we have demonstrated that using two simple markers, like waist circumference and fasting glucose, both capable of being measured in Primary Care, can help to identify glucose metabolism abnormalities and/or IR people. In fact 55.3% of the study group has hyperglycemia and/or IR whereas 64.3% of the control group shows normal glucose metabolism and/or no IR. In addition we find a prevalence of T2DM of 16.7% in this population. If we had considered subjects with T2DM treated with insulin, excluded by protocol in the present study, this percentage would significantly have increased.

This is the first study to analyze the prevalence of IGT and IFG for a large population managed in Primary Care centres throughout Spain. The level of participation in all the regions of Spain was similar, thereby indicating that there was no bias in the sample. However, the observed differences between the characteristics of the subjects that agreed to participate when compared to those who refused to cooperate, are a potential weakness of the present study. There were more non-participants among males, older people, patients with cardiovascular disease, family history of T2DM, known T2DM and dyslipidaemia. These differences could potentially limit extrapolation of the results to the Spanish population older than 45 years assigned to Primary Care centres. Nevertheless, the groups were fairly comparable for characteristics such as weight, height and blood pressure, and even in characteristics such as capillary glycaemia the differences were not clinically relevant.

Our results are consistent with those observed in the Spanish regional studies (8-14), in which IGT prevalence was between 7.2 and 17.1%; however our sample was representative of the entire Spanish population older than 45 years. In France, an observational study done in Primary Care and using fasting glucose as a diagnostic test, found a prevalence of IFG of 22%, which is quite similar to our result in which the prevalence of IFG plus IGT was 27.4% (21). However, in the French study the prevalence of undiagnosed diabetes, 0.67%, was lower than in our study, meaning that diabetes screening in Primary Care in France may be better implemented than in Spain. In contrast with these studies, a study based on Irish population also done in Primary Care encountered a prevalence rate for IFG and/or IGT of just 3.9% (22).

Although there is no consensus about the rate of progression to diabetes of both IFG and IGT, it is reasonable to assume that a majority of these subjects, especially those who are older, overweight, and have other diabetes risk factors, will develop diabetes over the next 10 years (23). If this hypothesis is confirmed, and the mortality rate is still the same, we could assume that the Spanish diabetes prevalence rate would result in a higher rate compared to the WHO's prediction, which is 39% in the global rate from 2000 to 2030.

This potential increase has been mainly attributed to a rise in new cases of T2DM, which in turn is driven by increasing obesity rates (24, 25) and ageing of the population (26). The increased migration of susceptible population, accompanied by shifts in lifestyle, has also added to increased prevalence of diabetes. In Spain, 8.5% of the population are immigrants, and most of them are relatively new to the country (27). Additionally, improved survival in people with diabetes might contribute to the increasing prevalence of the disease.

Another important aspect is that people with IFG and IGT have modestly increased CVD risk, and this becomes progressively greater with diabetes. Although there is a controversy about whether prediabetic states are *per se* independent risk factors (28-30) or their risk is due to their association with other cardiovascular risk factors (e.g., low HDL cholesterol, hypertension, and elevated triglycerides), early identification and treatment of these risk factors could prevent clinical vascular events in this population.

Late diagnosis of T2DM is still an unsolved problem in Primary Care, and diabetes remains frequently undiagnosed until complications appear (31), in fact, in our study 5.4% of the sample had undiagnosed diabetes. We have shown that two simple markers, both easy to use by Primary Care physicians, can help to identify subjects who have diabetes, IGT, IFG or IR.

In summary, we have found that in Spain the prevalence of IFG and IGT in the population older than 45 years assigned to Primary Care centres is high, and similar to the French population. This high prevalence predicts higher rates of diabetes prevalence than WHO's estimation. The combination of fasting glucose and waist circumference measurement could be an effective and easy to use tool to identify those subjects at risk of having any glucose metabolism alterations.

REFERENCES

1. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002; 25: 894-9.
2. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care 2004; 27: 201-7.
3. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.
4. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; 27: 17-20.
5. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National

Health and Nutrition Examination Survey 1999–2002. Diabetes Care 2006; 29: 1263-8.

6. Mooy JM, Grootenhuis PA, De Vries H, et al. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. Diabetes Care 1995; 18: 1270-3.
7. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183–97.
8. De Pablos Velasco PL, Martínez Martín FJ, Rodríguez-Pérez F, et al. Prevalence and determinants of diabetes mellitus and glucose intolerance in Canarian Caucasian population - comparison of the ADA and the 1985 WHO criteria. The Guia Study. Diabet Med 2001; 18: 235-41.
9. Botas P, Delgado E, Castaño G, et al. Comparison of the diagnostic criteria for diabetes mellitus, WHO-1985, ADA-1997, WHO-1999 in the adult population of Asturias (Spain). Diabet Med 2003; 20: 904-8.
10. Tamayo MB, Faure E, Roche A, et al. Prevalence of diabetes mellitus and impaired glucose tolerance in Aragon, Spain. Diabetes Care 1997; 20: 534-6.
11. Bayo J, Sola C, García F, et al. The prevalence of non-insulin dependent diabetes mellitus in Lejona (Vizcaya, Spain). Med Clin (Barc)1993; 101: 609-12.
12. Franch J, Álvarez JC, Álvarez F, et al. Epidemiology of diabetes mellitus in the Leon province. Med Clin (Barc) 1992; 98: 607-11.
13. Castell C, Tresserras R, Serra J, et al. Prevalence of diabetes in Catalonia (Spain): an oral glucose tolerance test-based population study. Diabetes Res Clin Pract 1999; 43: 33-40.
14. Goday A. Epidemiología de la diabetes mellitus y sus complicaciones no coronarias. Rev Esp Cardiología 2002; 55: 657-70.
15. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation. Geneva: World Health Organization, 1999.
16. Matheus DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.
17. Ascaso JF, Pardo S, Real JT, et al. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care 2003; 26: 3320-5.
18. Tormo MJ, Dal-Ré R, Pérez G. Ética e investigación epidemiológica: principios, aplicaciones y casos prácticos. Murcia: Sociedad Española de Epidemiología, 1998.
19. International guidelines for ethical review of epidemiological studies. Geneva: Council of International Organizations of Medical Sciences, 1991.
20. The expert committee on the diagnosis and classification of diabetes. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-7.
21. Cogneau J, Balkau B, Simon D. Assessment of diabetes screening by general practitioners in France: the EPIDIA. Diabet Med 2006: 803-7
22. Smith SM, Holohan J, McAuliffe A, Firth RG. Irish diabetes detection programme in general practice. Diabet Med 2003; 20: 717-22.
23. Nathan DM, Davidson MB, DeFronzo RA, et al; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care Diabetes Care 2007; 30: 753-9.
24. Martinez JA, Moreno B, Martinez-Gonzalez MA. Prevalence of obesity in Spain. Obes Rev 2004; 5: 171-2.
25. Basterra-Gortari FJ, Bes-Rastrollo M, Seguí-Gómez M, Forga L, Martínez JA, Martínez-González MA. Trends in obesity, diabetes mellitus, hypertension and hypercholesterolemia in Spain (1997-2003). Med Clin (Barc) 2007; 129: 405-8.
26. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414: 782-7.
27. http://www.msc.es/estadEstudios/estadisticas/docs
28. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyorala K, DECODE Study Group, European Diabetes Epidemiology Group. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor: the DECODE Study. Diabetologia 2004; 47: 2118-28.
29. Balkau B, Forhan A, Eschawege E. Two hour plasma glucose is not unequivocally predictive for early death in men with impaired fasting glucose: more results from the Paris Prospective Study. Diabetologia 2002; 45: 1224-30.
30. Meigs JB, Nathan DM, D'Agostino RB Sr, William PW. Fasting and post-challenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002; 25: 1845-50.
31. Screening for type 2 Diabetes. American Diabetes Association. Diabetes Care 2004; 7: S11-4.