

An Evaluation of Glucose Tolerance in Essential Hypertension

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Purpose: This study aimed to determine the impaired glucose tolerance and diabetes prevalence in patients with essential hypertension (HT) and to compare the developed microvascular complications of these groups. **Materials and Methods:** An oral glucose tolerance test (OGTT) was performed on 338 essential hypertensive cases and glucose tolerances were classified according to ADA-2002 criteria. **Results:** Of the 338 cases, 32 people had diabetes (DM, 9.46%), 78 people had glucose intolerance (IGT, 23.1%), and 228 people had only hypertension but not IGT and DM (67.4%). Both the mean ages of the DM group (56.9 ± 6.7 years, $p = 0.002$) and IGT group (56.3 ± 8.4 years, $p = 0.003$) were older than the mean age of the control group (51.1 ± 6.4 years). The risk of IGT development was found to be four times greater in male cases than female cases when compared to the control group ($p = 0.004$, add ratio = 4.194). There were no significant differences in the body mass indexes (BMI's), hypertension durations, and microvascular complications between the groups. **Conclusion:** In conclusion, the risk of IGT and DM development in hypertensive cases increases with aging and longer hypertension duration. The risk of IGT development in hypertensive cases is four times more in males.

Key Words : Diabetes mellitus, glucose tolerance, epidemiology, hypertension, insulin resistance

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INTRODUCTION

It is thought that insulin resistance syndrome leads to impaired glucose tolerance, dyslipidemia, hypertension, and impaired fibrinolytic activity.¹ Insulin sensitivity is lower in patients with essential hypertension when compared with normotensive patients.² The insulinemic response to a glucose load is greater among patients with essential hypertension. An impaired glucose uptake in cells accompanies this situation.³ Also, according to the 2002 reports of the American Diabetes Association (ADA), essential hypertension is accepted as the major risk factor for the development of type 2 diabetes mellitus.⁴

We aimed to determine the impaired glucose tolerance and diabetes prevalence in patients with essential hypertension and to compare the developed microvascular complications of these groups.

MATERIALS AND METHODS

We enrolled 338 subjects in this study from 1998-2002. Blood pressure (BP) was measured two times in the seated position after about 10 minutes of rest with a standard manual mercury sphygmomanometer (for nonobese subjects) and an 18 × 42 cm extra large cuff (for obese subjects). The recorded pressure of the two measurements was averaged. Subjects with a systolic and diastolic BP equal to or exceeding 140/90 mmHg, and those who had used BP lowering medications were considered to have hypertension (Table 1). Secondary causes of hypertension in all patients were excluded, as far as possible, by the findings of the following clinical examinations: serum urea, creatinine, electrolytes, thyroid-stimulating hormone (TSH) and free T4 concentrations, urinary metanephrine, and an over-

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night 1 mg dexamethasone suppression test.

The oral glucose tolerance test (OGTT) was performed on 338 essential hypertensive cases. The results were classified according to ADA 2002 criteria.⁴

We measured the values 2 hours after we had given 75 gr of glucose to each patient. Those patients whose 2 hour plasma glucose (2h PG) level was 140-200 mg/dL were evaluated as having impaired glucose tolerance (IGT), those whose fasting plasma glucose (FPG) level was ≥ 126 mg/dL or 2h PG was ≥ 200 mg/dL were evaluated as having type 2 diabetes mellitus (DM), and finally those whose FPG was < 126 mg/dL and 2h PG was < 140 mg/dL were evaluated as having normal glucose tolerance. None of the cases had the typical clinical character-

istics of DM as their fasting glucose levels were in the normal range (80-125 mg/dL). None of the patients had been taking any oral antidiabetic medications or following a calorie restricted diet before the laboratory evaluation.

We revealed retinopathies and nephropathies in all patients by performing ophthalmologic examinations and kidney function tests (creatinin, creatinin clearance, and microalbuminuria) respectively. 30 cases consisted of the control group. They were chosen from 228 cases of essential hypertension, but not impaired glucose tolerance, diabetes, anemia, thyroid disease, neurologic disorders and malignancies, furthermore, from those cases that had complete results from all parameter tests. All data were recorded to SPSS 10.0 and evaluated by a Chi-square test, one way variance analysis, a correlation test, and logistic regression analysis.

Table 1. Distribution of Antihypertensive Medications According to Groups

Antyhypertensive medication	Control group (%)	IGT group (%)	DM group (%)
Diuretics	36	32	20
α -blockers	16	30	31
β -blockers	20	9	9.3
Calcium channel blockers	36	40	34
ACEI's	60	40	60
AT II blockers	10	28	22

IGT, impaired glucose tolerance; ACEI, angiotensin-converting enzyme inhibitor.

RESULTS

Out of all the enrolled patients, 32 people had diabetes (DM, 9.46%), 78 people had glucose intolerance (IGT, 23.1%), and 228 people had only hypertension without impaired glucose tolerance or diabetes (control, 67.4%). The features of these groups (the control group being 30 cases chosen from the 228 cases) are shown on Table 2.

When compared with the mean age of the control group

Table 2. Features and Comparison of the Mean Values of the Control, IGT and DM Groups

Control group	IGT group	DM group	Significant
Cases (n)	30	78	32
Age (yr)	51.1 \pm 6.4	56.3 \pm 8.4	56.9 \pm 6.7 $p = 0.003$
Sex (M / F)	14 E, 16 K	17 E, 61 K	12 E, 20 K $p = 0.004$
HT duration (yr)	7.6 \pm 5.3	8.9 \pm 6	10.8 \pm 7.3 NS
Diabetes history in family (yes / no)	5 / 25	19 / 59	3 / 29 NS
BMI (kg / m ²)	30.4 \pm 4.8	31.1 \pm 4.7	30.17 \pm 4.1 NS
Fasting plasma glucose (mg / dL)	99.1 \pm 14	100.9 \pm 13	115.5 \pm 13 NS
HbA1c (%)	-	5.4 \pm 0.9	5.8 \pm 0.9 NS
Insulin (IU)	12.9 \pm 2.9	11.4 \pm 1.2	9.8 \pm 1.2 NS
HOMA-R	3.1 \pm 0.8	2.2 \pm 0.6	2.7 \pm 0.4 NS
Systolic blood pressure (mmHg)	158.5 \pm 22	168.9 \pm 22	161.4 \pm 23 NS
Diastolic blood pressure (mmHg)	103.1 \pm 10	101.7 \pm 12.5	98.5 \pm 11 NS
Tryglycerid (mg / dL)	171.7 \pm 74	188.7 \pm 100	182.1 \pm 84 NS
Cholesterol (mg / dL)	219.1 \pm 40	227.6 \pm 50	223.1 \pm 36 NS
LDL-cholesterol (mg / dL)	138.8 \pm 31	141.9 \pm 45	136.7 \pm 32.6 NS
HDL-cholesterol (mg / dL)	45.1 \pm 8.5	48.3 \pm 11.4	47.9 \pm 10.1 NS
Uric acid (mg / dL)	6.1 \pm 5.1	4.8 \pm 1.5	5.1 \pm 2.2 NS
Creatinin (mg / dL)	0.97 \pm 0.2	0.89 \pm 1	0.93 \pm 0.2 NS
Creatinin clearance (mL / dk)	95.3 \pm 29	91.8 \pm 29	86 \pm 23 NS
Microalbuminuria (mg / day)	29.8 \pm 33	29.2 \pm 23	30.5 \pm 10.4 NS

IGT, impaired glucose tolerance; DM, diabetes mellitus; HT, hypertension; BMI, body mass index; AbA1c, hemoglobin A1c; HOMA-R, homeostasis model assessment index ratio; LDL, low density lipoprotein; HDL, high density lipoprotein.

(51.1 ± 6.4 years), both the mean ages of the DM group (56.9 ± 6.7 years; $p = 0.002$) and IGT group (56.3 ± 8.4 years; $p = 0.003$) were older. The age variance among these three groups ($p = 0.003$) was highly significant according to the one way variance analysis (Fig. 1).

In the DM group there were 12 men and 20 women, in the IGT group there were 17 men and 61 women, and in the control group there were 14 men and 16 women (Fig. 2).

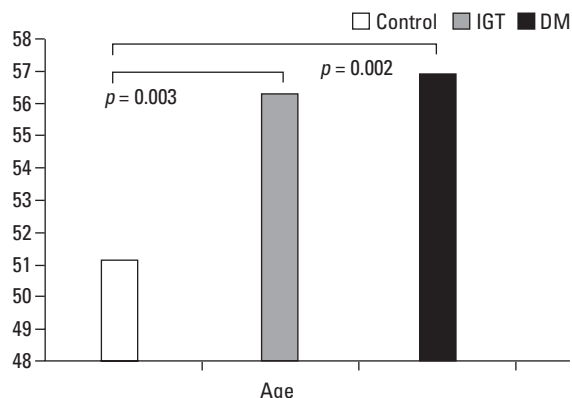


Fig. 1. Mean ages of three groups. IGT, impaired glucose tolerance; DM, diabetes mellitus.

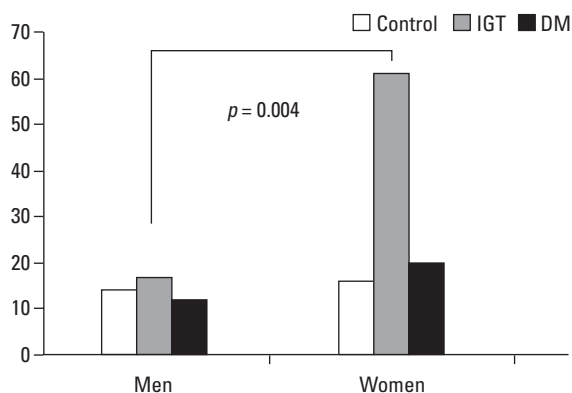


Fig. 2. Number of male and female subjects in three groups. IGT, impaired glucose tolerance; DM, diabetes mellitus.

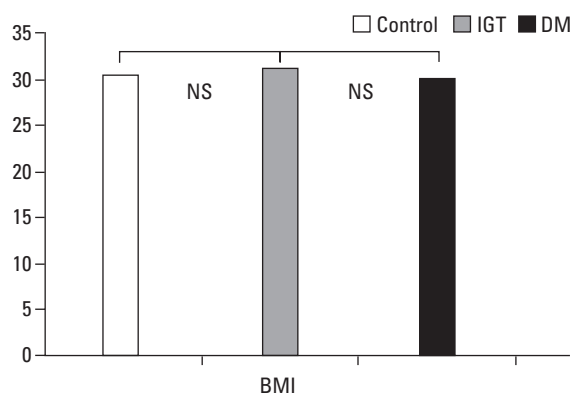


Fig. 3. Means of BMI of three groups. IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; NS, statistically non-significant.

According to the logistic regression analysis, the risk of IGT development was found to be four times greater in male cases than in female cases when compared to the control group ($p = 0.004$, odd ratio = 4.194).

The body mass indexes (BMIs) of the groups were as follows: 30.17 ± 4.1 kg/m² in the DM group, 31.1 ± 4.7 kg/m² in the IGT group, and 30.42 ± 4.8 kg/m² in the control group. There was no significant difference in the BMIs among these groups (Fig. 3).

Patients had hypertension for 10.8 ± 7.3 years in the DM group, 8.9 ± 6 years in the IGT group, and 7.6 ± 5.3 years in the control group (Fig. 4). There was no statistically significant difference among these durations.

5 patients in the DM group, 19 patients in the IGT group, and 3 patients in the control group had a history of diabetes in their families; these values were not statistically different. These results are given in Fig. 5.

Among these groups, a significant difference could not be evaluated from the values of FPG, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, uric acid, hemoglobin A1c (HbA1c), homeostasis model assessment index ratio (HOMA-R), mean systolic and diastolic blood pressures (Table 2).

The ophthalmologic examinations of all patients were

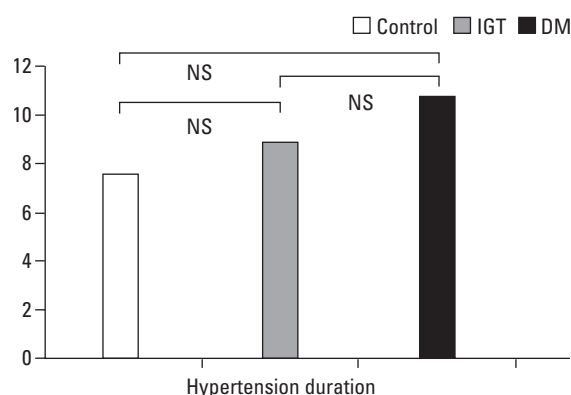


Fig. 4. Duration of hypertension in three groups. IGT, impaired glucose tolerance; DM, diabetes mellitus; NS, statistically non-significant.

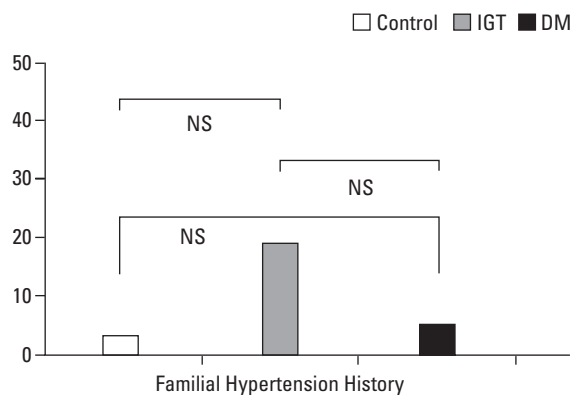


Fig. 5. Number of patients having a familial hypertension history in three groups. IGT, impaired glucose tolerance; DM, diabetes mellitus; NS, statistically non-significant.

evaluated regarding hypertensive retinopathy and diabetic retinopathy. Diabetic retinopathy was not found in both the DM and IGT groups. Hypertensive retinopathy, which had been detected in all patients, was at greater levels in both the DM and IGT groups ($p = 0.039$).

The microalbuminuria (MA) level (30-300 mg/day), which had been used as the nephropathy parameter, was 30.5 ± 10.4 mg/day in the DM group, 29.2 ± 23 mg/day in the IGT group, and 29.8 ± 33 mg/day in the control group. There were no significant differences among these results. For all three groups, there was no significant relationship between the presence of MA and hypertensive retinopathy or BMI.

DISCUSSION

In the series of studies, the presence of a family history of diabetes, impaired glucose tolerance, hypertension (HT), and an increase in BMI were found to be independent risk factors for the development of diabetes.⁴⁻⁶ It has been reported that changing ones life style (to lessen obesity, increasing physical activities, changing nutritional habits) causes a serious decrease, or at least a delay, in the development of diabetes.^{7,8}

The morbidity and mortality of cardiovascular system (CVS) disorders are increased in the DM group. They are also increased in the impaired fasting glucose (IFG) and IGT groups. Thus, the detection of IFG and IGT in patients has more diagnostic value.⁹⁻¹¹ As a result of these studies, investigations have been held in recent years to find a better glucose cut off value to determine the risk of diabetes.^{5,10-12}

Obesity, smoking, IGT, hyperlipidemia, and HT are the risk factors for cardiovascular disease.^{13,14} It has been determined that hyperinsulinemia and an impaired glucose uptake in muscle cells are seen in essential HT.³

We aimed to investigate IGT and DM in patients with essential hypertension. When we evaluated the OGTT results of 338 cases by ADA 2002 criteria, we found that 23.1% had IGT and 9.46% had DM (not known before).

From epidemiological studies DM and IGT prevalences have been found to be 6-15% and 15-24% respectively, both of which have greatly increased in the last few decades.^{6,15-18} According to the Turkish Diabetes Epidemiology Prevalence Study (TURDEP),¹⁹ DM prevalence is 7.2%, IGT prevalence is 6.7%, and HT prevalence is 29% in the general public. Among the people who have HT, DM prevalence is 16.1%, and IGT prevalence is 11.6%. In another investigation from our country,²⁰ DM prevalence is 10.58% and IGT prevalence is 24.11% according to ADA criteria. From these results, it is obvious that the DM and IGT prevalences of hypertensive patients are not very different from epidemiological prevalences.

The increase in DM prevalence as a result of modernization and longer life spans is important.^{6,16} Similar to these studies, in our study the mean ages of the IGT and DM groups were

significantly higher than that of the control group ($p = 0.003$). This supports the findings that a decrease in insulin sensitivity in a middle aged person will lead to obvious impaired glucose tolerance in older ages.²¹ Age and glucose levels are the independent risk factors that decrease the glomerular filtration rate. Thus, investigating IGT, especially in patients who have HT, is a possible determinant of renal failure due to aging.²²

In previous studies it has been reported that DM, IGT, and IFG prevalences are found to be higher in males.^{5,6,12,15} Macrovascular diseases are more frequent in female diabetics.¹⁷ Also, in women who have HT, an important relationship between IGT and obesity (which are cardiovascular risk factors) exists.¹³

In our study, the risk of IGT development was four times higher in male patients than in female patients when compared with the control group.

An increase in obesity in developed countries in the last 3 decades and the risk of DM development due to obesity and its duration has led to the suggestion of forming the term diabetes.⁶ IGT prevalence is also high in seriously obese children and adolescents, and in these groups, serious obesity plays a role in type 2 DM pathogenesis.²³ Obesity is also a serious risk factor for cardiovascular diseases.¹¹

In our study, there was no significant difference between the BMIs of the groups, but all BMIs were above the cut off value for obesity, which causes a risk for IGT, DM, cardiovascular diseases and HT. Although a significant difference in the levels of lipids, FPG, HOMA-R, and BMI could not be evaluated among the groups, we think that BMI values, when above the cut off values, are important for glucose metabolism disturbance which develops in HT cases. HT prevalence is high in DM and IGT groups.^{5,11,13,15} It has been determined that 2h PG levels have damaging effects on the endothelial functions in patients who have HT.²⁴

In the current study, although the result was not significant in both the DM group and IGT group, the hypertension durations were longer than that of the control group. It seems that age and the length of HT duration increase the probability of having IGT.

The frequencies of retinopathy and nephropathy have been shown to have a direct relationship with fasting glucose and 2h postprandial plasma glucose.²⁵ We didn't determine diabetic retinopathy in either the DM or IGT group.

The hypertensive retinopathy level was in a higher state in both groups ($p = 0.039$, Grade II or III). This incidence may be explained by longer hypertensive durations.

The development of MA, which is important for the diagnosis and classification of nephropathy, increases with long term hyperglycemia and subdiabetic glycemia.^{26,27} The MA level was not significantly different among the groups, but the mean values of all three groups were at the minimal cut off value of MA. This can be explained by hypertension which causes endothelial damage. MA is reported as the strongest determinant of cardiovascular mortality in patients having type 2 DM,

IFG/IGT, and insulin resistance.²⁸

In conclusion, we think that the risk of IGT and DM development in HT cases increases with aging and longer HT duration. The risk of IGT development in hypertensive cases is four times higher in males.

REFERENCES

- Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA* 2002;287:2081-9.
- Natalucci S, Boemi M, Fumelli P, Testa I, Fumelli D, Burattini R. One- and two- compartment minimal models detect similar alterations of glucose metabolism indexes in hypertension. *Metabolism* 2000;49:1529-36.
- Gouveia LM, Paccola GM, Torquato MT, Menezes FO, Piccinato CE, Foss MC. Peripheral glucose metabolism in patients with essential hypertension. *Horm Metab Res* 2000;32: 35-9.
- American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care* 2002; 25 (Suppl 1):S21-4.
- von Eckardstein A, Schulte H, Assmann G. Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American Diabetes Association. *Prospective cardiovascular Münster. J Clin Endocrinol Metab* 2000;85:3101-8.
- Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 2002;25:829-34.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.
- Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.
- Barzilay JI, Spiekerman CF, Kuller LH, Burke GL, Bittner V, Gottdiener JS, et al. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care* 2001;24:1233-9.
- Rodriguez BL, Abbott RD, Fujimoto W, Waitzfelder B, Chen R, Masaki K, et al. The American Diabetes Association and World Health Organization classifications for diabetes: their impact on diabetes prevalence and total and cardiovascular disease mortality in elderly Japanese-American men. *Diabetes Care* 2002;25:951-5.
- Lim SC, Tai ES, Tan BY, Chew SK, Tan CE. Cardiovascular risk profile in individuals with borderline glycemia: the effect of the 1997 American Diabetes Association diagnostic criteria and the 1998 World Health Organization Provisional Report. *Diabetes Care* 2000;23:278-82.
- Shaw JE, Zimmet PZ, Hodge AM, de Courten M, Dowse GK, Chitson P, et al. Impaired fasting glucose: how low should it go? *Diabetes Care* 2000;23:34-9.
- Borde-Perry WC, Campbell KL, Murtaugh KH, Gidding S, Falkner B. The association between hypertension and other cardiovascular risk factors in young adult African Americans. *J Clin Hypertens (Greenwich)* 2002;4:17-22.
- Simon NR, Frishman WH. Diabetes mellitus in the aging: epidemiologic and therapeutic considerations. *Am J Geriatr Cardiol* 1992;1:22-36.
- King H, Djumaeva S, Abdullaev B, Gacic Dobo M. Epidemiology of glucose intolerance and associated factors in Uzbekistan: a survey in Sirdaria province. *Diabetes Res Clin Pract* 2002;55:19-27.
- Lam TH, Liu LJ, Janus ED, Lam KS, Hedley AJ; Hong Kong Cardiovascular Risk Factor Prevalence Study Steering Committee. Fibrinogen, other cardiovascular risk factors and diabetes mellitus in Hong Kong: a community with high prevalence of type 2 diabetes mellitus and impaired glucose tolerance. *Diabet Med* 2000;17:798-806.
- Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes. *Diabet Med* 2000;17:835-40.
- Ribstein J, Du Cailar G, Mimran A. Glucose tolerance and age-associated decline in renal function of hypertensive patients. *J Hypertens* 2001;19:2257-64.
- Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). *Diabetes Care* 2002;25:1551-6.
- Ozkan Y, Donder E, Dogan H, Demir A, Yalıtız M, Sokmen S. Hipertansif hastalarda tip 2 diabetes mellitus ve bozulmuş glukoz tolerans sıklığı. *Turkish Journal of Endocrinology and Metabolism* 1999;3(2 Suppl 1):129.
- 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* 2002;25(Suppl 1):S5-20.
- Ribstein J, Du Cailar G, Mimran A. Glucose tolerance and age-associated decline in renal function of hypertensive patients. *J Hypertens* 2001;19:2257-64.
- Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802-10.
- Tomiyaama H, Kimura Y, Okazaki R, Kushiro T, Abe M, Kuwabara Y, et al. Close relationship of abnormal glucose tolerance with endothelial dysfunction in hypertension. *Hypertension* 2000;36:245-9.
- Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, et al. Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes Care* 2000;23:1113-8.
- Meigs JB, D'Agostino RB, Nathan DM, Rifai N, Wilson PW; Framingham Offspring Study. Longitudinal association of glycemia and microalbuminuria; the Framingham Offspring Study. *Diabetes Care* 2002;25:977-83.
- Sosenko JM, Hu D, Welty T, Howard BV, Lee E, Robbins DC. Albuminuria in recent-onset type 2 diabetes. *Diabetes Care* 2002;25:1078-84.
- Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683-9.