Section: Medicine

Original Research Article

PROFILE OF PERIPHERAL ARTERIAL DISEASE AND RISK FACTORS IN PEOPLE WITH TREATMENT NAIVE TYPE 2 DIABETES MELLITUS AND PRE-DIABETES.

Mir Khalid Mairaj[1], Nazir Ahmad Pala[2], Mohd Ismail[3], Shabir Ahmad Bhat[4]

[1]*MD internal Medicine Department of Medicine, Government Medical College, Srinagar, J&K, India.*
[2]*Associate professor Department of Medicine, Government Medical college Srinagar, J&K, India.*
[3]*Professor Department of Medicine, Government Medical college, Srinagar, J&K, India.*
[4]*Professor Department of Radiodiagnosis, Government Medical College, Srinagar, J&K, India.*

Received *: 06/03/2024*
Received in revised form *: 14/05/2024*
Accepted *: 30/05/2024*

Corresponding Author:
Dr. Mir Khalid Mairaj
MD internal Medicine Department of Medicine, Government Medical College, Srinagar, J&K, India.
Email:khalidmehraj94@gmail.com.

DOI: 10.5530/ijmedph.2024.2.118

Source of Support: Nil,
Conflict of Interest: Nonedeclared

Int J Med Pub Health
2024; 14 (2); 620-624

ABSTRACT

Background: Diabetes mellitus has been found to be a progenitor of peripheral arterial disease (PAD) in various epidemiological studies. Whether chronic hyperglycemia per se or altered levels of intermediate conventional risk factors in these people are responsible for increased risk of PAD, is a matter of debate. There is little data about the profile of peripheral arterial disease in people with treatment naive diabetes and prediabetes in Asian population. **Objectives:** The study aimed to determine the frequency of early PAD among people with newly detected treatment naive diabetes and prediabetes attending a tertiary care public hospital. The study further aimed to determine the risk factors associated with peripheral arterial disease and to investigate whether such risk factors in these people might help to explain their increased risk of PAD.

Materials and Methods:65 consecutive people with treatment naive type 2 diabetes (T2DM) with an equal number of people with prediabetes, attending a tertiary care centre, diagnosed as per standard criteria, were enrolled in a non-randomised prospective design. The presence of peripheral arterial disease was determined by ankle-brachial index (ABI). Risk factor analysis for peripheral arterial disease in both the groups was carried out. Statistical significance was considered with p value of <0.05.

Results:7(10.8%) people among newly diagnosed treatment naïve type 2 diabetes and 2 (3.1%) with prediabetes had PAD (ABI score<0.9), age (p <0 .001), high plasma glucose/HbA1c (p<0.001), BMI (p<0.001), total cholesterol (p <0.001), albuminuria and hypertension (p<0.001), were found to be strongly associated with early vasculopathy.

Conclusion: Peripheral arterial disease is a frequent complication among newly diagnosed treatment naive people with T2DM and to a lesser extent in people with prediabetes. Various anthropometric, clinical, biochemical and metabolic factors in people with hyperglycemia could account for increased frequency of PAD in these people.

Keywords: Diabetes, Pre-Diabetes, Peripheral arterial disease,Treatment naive Diabetes.

INTRODUCTION

Peripheral arterial disease (PAD) is characterized by decreased blood flow to the limbs, due to an obstruction or narrowing of the vessel tributaries.[1]PAD is strongly associated with the development and progression of complications related to diabetic foot; poor wound healing, impaired perfusion, deformity and superimposed infections.[2]PAD is linked to higher cardiovascular morbidity and mortality, irrespective of gender or its clinical presentation (symptomatic or asymptomatic), especially in people who need peripheral revascularization.[3]Diabetes mellitus is associated

with more frequent, severe and diffuse PAD relative to people without diabetes. The basis for higher frequency and severity of PAD in people with hyperglycemia is a matter of debate, however some of the effect may be related to alteration of conventional cardiovascular risk factors, like hypertension, cigarette smoking, triglycerides, cholesterol, and albuminuria compared to people without diabetes.[4]People with prediabetes have increased risk of coronary artery disease and atherosclerosis compared to normoglycemic subjects.[5,6]Although, several population based studies have revealed an elevated cardiovascular risk in people with prediabetes,[7]there is scarcity of data with regard to the risk of PAD in these people. PAD remains undetected, as initially most of the patients are asymptomatic with ankle brachial index < 0.9. Early detection or screening of peripheral arterial disease (PAD) with timely intervention or institution of treatment among people with hyperglycemia will definitely reduce diabetic foot ulcers and eventually the frequency of amputations. This could also help to devise a comprehensive foot care programme to minimize risk of morbidity and mortality associated with PAD.

The study is aimed to determine the frequency of early PAD among people with newly detected treatment naive diabetes and prediabetes attending a tertiary care public hospital. The study further aimed to determine the risk factors associated with peripheral arterial disease and to investigate whether raised levels of such risk factors in these people might help to explain their increased risk of PAD.

MATERIAL AND METHODS

Study population

This study was conducted in the Department of Internal Medicine at a tertiary care hospital in North India over a period of 2 years. Sixty-five consecutive patients with newly detected treatment naive type 2 diabetes mellitus with equal number of people with prediabetes (total=130), were included in the study. The study was approved by the Institutional Ethics Committee and informed consent was obtained from all the study participants. Patients with newly diagnosed treatment naive T2DM and prediabetes with age ≥ 20 years to 60 years were enrolled. T2DM was diagnosed in accordance with American Diabetic Association (ADA) criteria, where any of the following criteria met as Fasting Plasma Glucose (FPG) ≥ 126 mg/dl or 2hr Plasma Glucose (2-h PG) ≥ 200 mg/dl during Oral glucose tolerance test (OGTT) or A1C ≥ 6.5% or a patient with classic symptoms of hyperglycemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dl. Prediabetes was diagnosed by (A1C ≥5.7% <6.5% or FPG of 100 - 125mg/dl or impaired glucose tolerance (IGT:2hr PG ≥140≤199).[8]

People with type 1 DM, people with serious diabetic complications like lower limb amputation, patients with any symptoms suggesting nephropathy and known smokers, were excluded from study.

Study protocol

Demographic details of patients like age, gender, and duration of diabetes, previous history of foot ulcer and history of any comorbidity, were recorded. Blood pressure was calculated as the mean of two measurements performed in a sitting position after 5 minutes of rest, using a random-zero sphygmomanometer. Individuals were considered hypertensive if they had a diastolic blood pressure ≥90 mmHg, had a systolic blood pressure≥140 mmHg, and/or were taking anti-hypertensive medication.[9]BMI was classified by WHO criteria for Asian population.[10]Vascular status of extremity was determined by ankle brachial index (ABI). Ankle-brachial pressure index(ABPI) was calculated by dividing Ultrasound Doppler assisted systolic blood pressure measured in the posterior tibial artery at the level of the ankle by the systolic blood pressure measured in the brachial artery on both sides(ABPI =Ankle systolic blood pressure/ Brachial systolic pressure).Peripheral arterial disease was labelled when ABI values of ≤0.89 were obtained (Normal 0.9-1.4).[11]

Metabolic parameters

Oral glucose tolerance test (OGTT) performed with 75g glucose dissolved in 250ml water after an overnight eight hour fast. Plasma glucose was estimated by enzymatic method using glucose oxidase and peroxidase on an automated chemistry analyzer (HITACHI-912). Glycated haemoglobin (HbA1C) was determined by high performance liquid chromatography (HPLC).Lipid parameters were analysed with commercially available enzymatic reagents (Audit Diagnostics, Ireland) adapted to the Hitachi 912 autoanalyzer. The Friedewald formula was used to calculate LDL cholesterol. The upper normal limit for reference population for fasting total cholesterol, LDL, HDL and TG were 200 mg/dl, 100 mg/dl, 40 mg/dl, and 150 mg/dl respectively. Serum creatinine was measured by kinetic alkaline picrate method; blood urea nitrogen by urease method, urinary albumin was determined by a radioimmunoassay technique (Immunotech, Prague, Czech Republic).

Statistical Analysis

The statistical software SPSS 20 (SPSS Inc, Chicago, Illinois, USA) was used to analyse data. Continuous variables were expressed as Mean ± SD and categorical variables as percentages. Student's independent t-test was employed for comparing continuous variables. Chi-square or Fisher's exact test, whichever appropriate, was used for comparison of categorical variables. All results have been described on 5% level of significance i.e. *P* value of <0.05 being considered as significant.

RESULTS

Among 130 patients (65 newly diagnosed treatment naive T2DM with equal number of people with prediabetes) recruited, peripheral arterial disease was detected in 7(10.8%) people with newly diagnosed treatment naive T2DM and 2(3.1%) in people with prediabetes. Mean (SD) age and BMI of people with T2DM with PAD was significantly higher (55.6±4.5 vs 42.3±7.5] years, p <0.001) and (28.2±3.0 vs 23.2±3.2 kg/m2, p<0.001) respectively compared to those without PAD. Mean (SD) total cholesterol (343.9±79.6 vs 216.5 ±55.2 mg/dl, p<0.001), FPG (246.3±56.1 vs 182.2±38.7 mg/dl, p<0.001), PPG (367.2±81.3 vs 292.6±57.0mg/dl, p<0.002) and HbA1c (10.1±0.6] vs 7.8±1.1], p<0.001) at presentation was significantly higher in people with PAD compared those without PAD. Frequency of hypertension (92.3% vs 30.8%, p<0.001) and albuminuria (76.9% vs 9.6%,p<0.001) was significantly higher in people with T2DM and PAD compared to those without PAD. [Table 1]

Similarly, people with prediabetes and PAD had significantly higher age and BMI (55.6±4.5 vs 45.9±8.4 years, p<0.001) and (25.6±2.0] vs 23.1±2.8] kg/m2,p<0.001) respectively. Mean (SD) total cholesterol (286.6±58.0 vs186.9± 37.7 mg/dl, p<0.001),FPG(120.8±1.9 vs 114.1±6.4 mg/dl, p<0.005),PPG(189.5±4.3 vs 166.9±16.4 mg/dl, p;0.001) and HbA1C (6.2± 0.1% vs 5.9±0.1 %, p<0.001) was significantly higher in people with PAD compared to those without PAD. Frequency of hypertension (100% vs 28%,p<0.001) and albuminuria(100% vs 3.5%,p<0.001, was significantly higher in people with peripheral arterial disease compared to those without peripheral arterial disease. [Table 2]

Table 1: Clinical and laboratory parameters of people with treatment naive type 2 diabetes mellitus with &without peripheral arterial disease(n=65)

Parameter	PAD(n=7)	without PAD (n=58)	*P* value
Age(years) [a]	55.6(4.52)	42.3(7.57)	**<.001**
Total cholesterol (mg/dl) [a]	343.9(79.67)	216.5(55.21)	**<.001**
(HbA1c %) [a]	10.1(0.695)	7.8(1.184)	**<.001**
FPG(mg/dl) [a]	246.3(56.19)	182.27(38.78)	**<.001**
PPG(mg/dl) [a]	367.2(81.37)	292.6(57.02)	**<.002**
BMI(kg/m^2) [a]	28.2(3.09)	23.2(3.29)	**<.001**
Hypertension(mmHg) [b]	6(92.3)	18(30.8)	**<.001**
Albuminuria [b]	5(76.9)	6(9.6)	**<.001**

[a]Data expressed as mean(SD), [b]Data expressed as n (%), FPG= Fasting plasma glucose, PPG= Postprandial plasma glucose

Table 2: Clinical and laboratory parameters of people with Pre-diabetes with & without peripheral arterial disease (n=65)

Parameter	PAD(n=2)	Without PAD (n=63)	P value
Age(years) [a]	55.6(4.52)	45.9(8.47)	**<.001**
Total cholesterol (mg/dl) [a]	268.6(58.05)	186.9(37.71)	**<.001**
(HbA1c %) [a]	6.28(0.138)	5.95(0.198)	**<.001**
FPG(mg/dl) [a]	120.8(1.91)	114.1(6.46)	**.005**
PPG(mg/dl) [a]	189.5(4.34)	166.9(16.49)	**.001**
BMI(Kg/m^2) [a]	25.6(2.03)	23.1(2.81)	**<.001**
Hypertension(mmHg) [b]	2(100)	18(28)	**<.001**
Albuminuria [b]	2(100)	2(3.5)	**<.001**

[a]Data expressed as mean(SD), [b]Data expressed as n(%), FPG= Fasting plasma glucose, PPG= Postprandial plasma glucose

DISCUSSION

Frequency of Peripheral arterial disease in people with newly diagnosed diabetes, Pre-diabetes.

Peripheral arterial disease (PAD) is a predominant cause of morbidity and mortality, especially affecting geriatric age group.[12-14]The frequency of PAD is multiple times higher in people with diabetes compared to age and gender matched healthy subjects, which could be because of alteration of multiple conventional cardiovascular risk factors in people with diabetes.[15]Chronic hyperglycemia has a pivotal role in development and progression of macrovascular complications,[16] and has been found to be strongly associated with acute coronary events.[17]This is in line with the previous studies reporting a high burden of vasculopathy in people with pre-diabetes and newly diagnosed type 2 diabetes.[18,19]In people with prediabetes, vascular disease might occur even before progressing to type 2 diabetes., similar findings with a rising trend of PAD from normal glucose tolerance to impaired glucose tolerance with a peak in people with diabetes, has been demonstrated in our study and several other studies in the past.[7,9]Frequency of peripheral arterial disease in our study among people with newly diagnosed diabetes was comparable to that reported from population based studies in the past,[20,21] but was considerably higher than that reported from

population based studies from Asia.[22,23]These differences in frequency may be because of the differences in the subject selection, sample size, and culture. Frequency of PAD in pre-diabetic group in our study was comparable to a population based study,[13]but was considerably lower than population based study in Scottish men and women.[24]This difference could be because of exclusion of smokers and relatively younger age of study subjects in our study. Since PAD can set in early in the course of hyperglycemic trajectory, targeted preventive strategies that identify individuals with pre-diabetes in the incipient stage for interventions would provide opportunities for vascular risk reduction,[25-27]considering that major benefits are likely to occur from early diagnosis and treatment.[28]

Risk factor Analysis of Peripheral arterial disease in people with Newly diagnosed Diabetes, Pre-diabetes.

The basis for preponderance of PAD in people with diabetes is still not clear. Whether chronic hyperglycemia per se or altered levels of intermediate conventional risk factors in these people are responsible for increased risk of PAD, is a matter of debate. Current study was designed to recruit people with newly detected treatment naïve DM and prediabetes to detect PAD in the incipient stage and to analyse the risk factors associated with PAD in these people. Insulin resistance syndrome,[29]has been found to be associated with the elevation in systolic blood pressure, triglycerides and higher prevalence of peripheral vascular disease, even has been demonstrated to be independent risk factor for PAD, irrespective of blood pressure and serum lipids.[30]In our study, people with diabetes and PAD were more hypertensive compared to those with pre-diabetes, as has been demonstrated previously.[31] Normoglycemic people with PAD have worse cardiovascular risk factor profile compared to those without PAD.[7]Similarly, people with diabetes/IGT and PAD have adverse risk factor profile compared to those without PAD, consistent with our study results.[32]However, after adjustment for systolic blood pressure and cholesterol, diabetic status was no longer a significant risk factor for PAD indicating that these two factors might be particularly important to explain the increased prevalence of PAD in people with diabetes/prediabetes, similar ,to observations made previously.[33]The mean age of people with diabetes/prediabetes and PAD was higher than those without PAD as demonstrated previously in population based prevalence studies.[7]

Onset and progression of macrovascular complications in people with hyperglycemia can be prevented, to some extent, by better glycemic control.[34] HbA1C level and postprandial blood glucose concentration has been found to be more important than the fasting plasma glucose concentration for the prevention of vascular complications in people with or without diabetes.[35]In our study, people with diabetes/prediabetes and PAD had higher HbA1c, mean fasting and postprandial plasma glucose compared to those without PAD, consistent with previous studies.[36,37] Postprandial hyperglycemia has been found to be an independent risk factor and superior predictor for macrovascular events compared to fasting plasma glucose concentration in numerous studies.[38] However, in some studies, a high fasting plasma glucose and HbA1C level has been found increase the risk of mortality from macrovascular event.[36,37]Plasma glucose levels in our study were based only on one single/average of two values (HbA1c was performed in all study subjects). Observing good glycemic control on multiple occasions may be important for predicting the onset and progression of vascular complications. However, further studies are needed to test the relationship of fasting/postprandial plasma glucose and PAD.

Obesity and metabolic syndrome have been found to have significant predilection for PAD with association as strong as conventional risk factors for PAD such as hypertension, hyperlipidemia, and diabetes,[39]as in our study, people with prediabetes/diabetes and PAD had higher BMI compared to those without PAD. Lastly, People with albuminuria with or without hypertension have multifold likelihood to have PAD (ABI < 0.9) than their counterparts without albuminuria,[40]similar to our study results.

CONCLUSION

Peripheral arterial disease is a frequent complication among newly diagnosed treatment naïve people with T2DM and prediabetes. Various anthropometric, clinical and biochemical parameters in people with hyperglycemia could account for increased frequency of PAD in these people. Early detection of PAD in people with newly diagnosed type 2 diabetes and prediabetes could help to devise a comprehensive foot care programme to minimize risk of morbidity and mortality associated with PAD. Further studies with larger cohort of people with newly diagnosed treatment naive type 2 diabetes mellitus and prediabetes should be undertaken to confirm our observations.

Limitations

The most important limitation of this study is small sample size. Studies with larger sample size in people with newly diagnosed diabetes and more importantly in people with prediabetes are required to look for early Peripheral arterial disease (PAD).

Conflict of interest: None.

REFERENCES

1. Hiatt WR, Goldstone J, Smith SC. Atherosclerotic Peripheral Vascular Disease Symposium II: Nomenclature for vascular diseases. Circulation 2008; 118: 2826.

2. Li CM, Chang CC, Chen CM, Lai LJ, Chen, MY. The Devil Is in the Detail: Prevention of Diabetic Foot Ulceration in Rural Areas Is Possible. Open Journal of Nursing 2013,3: 257-264.
3. Dawson DL, Hiatt WR, Creager MD. Peripheral Arterial Disease Medical Care and Prevention of Complications - Prev. Cardiol. 2002; 5:119-130.
4. Paisey RB, Arredondo G, Villalobos A, Lozano O, Guevara L, Kelly S. Association of differing dietary, metabolic and clinical risk factors with macrovascular complications of diabetes: a prevalence study of 503 Mexican type II diabetic subjects. Diabetes Care 1984; 7:421–427.
5. Kurihara O, Takano M, Yamamoto M, Shirakabe A, Kimata N, Inami T, et al. Impact of pre-diabetic status on coronary atherosclerosis: A multi vessel angioscopic study. Diabetes Care 2013; 36:729-33.
6. Ceriello A. Impaired glucose tolerance and cardiovascular disease: The possible role of post-prandial hyperglycemia. Am Heart J 2004; 147:803-7.
7. Premalatha G, Markovitz J, Shanthirani S, Mohan V, Deepa R. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population. Diabetes Care 2000; 23: 1295- 1300.
8. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2019 Jan; 37(Supplement 1): S81 S90
9. 1999 World Health Organisation- International Society of Hypertension: Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999; 17:151–183.
10. Appropriate BMI for Asian population and its implications for policy and intervention strategies.WHO expert consultation. Lancet 2004; 363:157-163.
11. European Stroke Organisation, Tendera M, Aboyans V, et al. – ESC Guidelines on the diagnosis and treatment of peripheral artery diseases. Eur Heart J. 2011; 32:2851-906.
12. Coni N, Tennison B, Troup M. Prevalence of lower-extremity arterial disease among elderly people in the community. Br J Gen Pract 1992; 42:149–152.
13. Federman DG, Trent JT, Froelich CW, Demirovic J, Kirsner RS: Epidemiology of peripheral vascular disease: a predictor of systemic vascular disease. Ostomy Wound Manage 1998; 44:58–62.
14. Hughson WG, Mann JI, Garrod E: Intermittent claudication: prevalence and risk factors. Br Med J 1978; 1:1379–1381.
15. Beach KW, Brunzell JD, Strandness DE. Prevalence of severe arteriosclerosis obliterans in patients with diabetes mellitus. Arteriosclerosis 1982; 2:275–280.
16. Tabák AG, Herder C, Rathmann W. Prediabetes: a high-risk state for diabetes development. Lancet 2012; 379:2279–90.
17. Deedwania P, Kosiborod M, Barrett E. Hyperglycemia and acute coronary syndrome. Circulation 2008; 117:1610–9.
18. Brannick B, Dagogo-Jack S, Prediabetes D-JS. Prediabetes and cardiovascular disease: pathophysiology and interventions for prevention and risk reduction. Endocrinol Metab Clin North Am 2018; 47:33–50.
19. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. ExpBiol Med 2016; 241:1323–31.
20. Melton LJ, Macken KM, Palumbo PJ, Elveback LR: Incidence and prevalence of clinical peripheral disease in a population- based cohort of diabetic patients. Diabetes Care 1980; 3:650–654.
21. Beks PJ, Mackaay AJC, de Neeling JN, de Vries H, Bouter LM, Heine RJ: Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn Study. Diabetologia 1995; 38:86–96.
22. Weerasuriya N, Siribaddana S, Dissanayake A, Subasinghe Z, Wariyapola D, Fernando DJ. Long-term complications in newly diagnosed Sri Lankan patients with type 2 diabetes mellitus. QJM 1998; 91:439–443.
23. Samanta A, Burden AC, Jagger C. A comparison of the clinical features and vascular complications of diabetes between migrant Asians and Caucasians in Leicester, U.K. Diabetes Res ClinPract 1991;14:205–213.
24. Jarrett RJ: Diabetes mellitus. In Epidemiology of Peripheral Vascular Disease F o w k e s FGR, Ed. Berlin, Springer-Verlag, 1991, p. 18: 7 – 193.
25. Koopman RJ, Mainous AG, Liszka HA. Evidence of nephropathy and peripheral neuropathy in US adults with undiagnosed diabetes. Ann Fam Med 2006; 4:427–32.
26. Cefalu WT. "Prediabetes": are there problems with this label? No, we need heightened awareness of this condition! Diabetes Care 2016; 39:1472–7.
27. Valabhji J, Barron E, Bradley D. Early outcomes from the English National Health Service Diabetes Prevention Programme. Diabetes Care 2020; 43:152–60.
28. Herman WH, Ye W, Griffin SJ. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: a simulation of the results of the Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION-Europe). Diabetes Care 2015; 38:1449–55.
29. Reaven GM: Role of insulin resistance in human disease. Diabetes 1988; 37: 1 5 9 5 – 1 6 0 7
30. Price JF, Lee AJ, Fowkes FGR. Hyperinsulinaemia:a risk factor for peripheral arterial disease in the non-diabetic general population. J CardiovascRisk 1997; 3:501–505.
31. ElhamFaghihimani, Ali Darakhshandeh, AwatFeizi, MasoudAmini.Evaluation of Peripheral Arterial Disease in Prediabetes. Int J Prev Med. 2014 Sep; 5(9): 1099–1105.
32. MacGregor AS; Price JF, HauCM, Lee AJ; Carson MN;FowkesFG. Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh Artery Study. Diabetes Care 1999;22(3):453–458.
33. Kannel WB, D'Agostino RB, Wilson PWF, Belanger AJ, Gagnon DR: Diabetes,fibrinogen, and risk of cardiovascular disease: the Framingham experience. Am Heart J 1990; 120: 3672–3676.
34. Stettler C, Allemann S, Jüni P. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J 2006; 152: 27 –38.
35. Levitan EB, Song Y, Ford ES. Is non-diabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004; 164: 2147 – 2155.
36. Hanefeld M, Koehler C, Schaper F. Postprandial plasma glucose is an independent risk factor for increased carotid intima–media thickness in non-diabetic individuals.Atherosclerosis 1999; 144: 229–235.
37. Sinnaeve PR, Steg PG, Fox KA. Association of elevated fasting glucose with increased short term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. Arch Intern Med 2009; 169: 402 – 409.
38. DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; 161: 397 – 405.
39. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 2004; 110:738–43.
40. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. ArteriosclerThrombVascBiol 1999; 19:1992–7.