Physiological study on Coronary Artery Disease Risk Factors: in Type 2 Diabetic Patients with Normal and Abnormal ECGs

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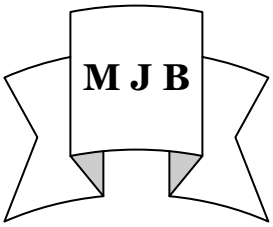

Abstract

The study sample size was 100 patients whom they have been recruited from Diabetes Unit in Marjan Teaching Hospital. We divided the sample into two groups; 88 with normal ECGs (group1) and 12 with abnormal ECG changes the (group2) .The range of their age 17-76 years old. The study includes nine risk factors that causes coronary artery disease (CAD) which are, High density lipoprotein (HDL-C), Low density lipoprotein (LDL-C), Total cholesterol (TC), Triglyceride (TG), Body mass index BMI, Age, Glucose, Duration and BP. Laboratory analyses of HDL-C, LDL-C, TC, TG, and glucose reveal, that, LDL-C correlated negatively with TGs and positively with HDL-C in the (group1), and TGs show positive correlation LDL-C size in (group2).The only positive significant correlation coefficient was the glucose in (group1), 394.36±40.82 compared to 244.75±54.4 (group2) with p value < 0.01. While 51%of all patients associated with hypertension. Duration of type 2 Diabetes Mellitus (T2DM) was 10-32 years for all patients.

Factor analyses for both groups variants result in: Variables analyses of component matrix of (group1) represent the risk factors on four categories while (group2) variables descript three risk factor categories, according to their performance percent on Coronary Artery Disease (CAD). Factor analysis reveals that; first, the factor of lipid profile had the great percentage of risk factor on CAD in both groups. Second; there was unobserved risk factors, one of these risk factors might be cytomegalovirus (CMV) which can infect pancreatic islet cells result in T2DM the main CAD risk factor. The group1 with abnormal electrocardiogram (ECG) changes reveals that 30.787% may be affected with CMV or even other reason rather than the common risk factors. Third; a glance to the percent, 42.16%, of first factor variance of the (group2) with normal ECGs, and 24.822% first factor variance of the (group1) match, tell more positive significant difference. Pearson correlation coefficients demonstrate no significant difference between all variables in both groups except glucose (394.36±40.8) expose an increase difference in group1 compared to (244.75±54.4) group2 with (P<0.01). And 51%of all patients associated with hypertension.

دراسة الجوانب الفسلجية للعوامل التي تشكل خطورة الإصابة بأمراض القلب لدى مرضى السكري/النوع الثاني الذين يظهرون وآخرين لا يظهرون تغيرات في تخطيط القلب.

الخلاصة

تناولت الدراسة ١٠٠ مريض بالسكري من النوع الثاني (T2DM) من وحدة مرضى السكري في مستشفى مرجان تراوحت أعمارهم بين١٧-٧٦ سنة. تم تقسيم المرضى بعد تشخيص تخطيط القلب إلى مجموعتين.المجموعة الأولى تضمنت ٨٨ مريض لم تظهر أية تغيرات في تخطيط القلب. أما المجموعة الثانية كانت ١٢ مريض بالقلب من خلال تشخيص التغيرات الحاصلة في تخطيط القلب.شملت الدراسة

العوامل التقليدية لخطورة الإصابة بأمراض القلب وهي العمر Age ومقياس كتلة الجسم BMI ، كولستيرول الدهون العالية الكثافة HDL-C, كولستيرول الدهون واطئة الكثافة LDL-C, الكولسترول الكلي TC،الدهون الثلاثيةالكلستيرات Glucose TG السكر ومدة المرض Dura, الضغط BP .

خلال البحث تبين إن كولستيرول الدهون واطئة الكثافة ترتبط سلبيا مع الدهون الثلاثية الكلستيرات وايجابيا مع كولستيرول الدهون عالية الكثافة HDL-C في المجموعة الأولى،بينما الدهون الثلاثية الكلستيرات ترتبط ايجابيا مع كولستيرول الدهون واطئة الكثافة LDL-C في المجموعة الثانية.

إن معامل الارتباط (correlation coefficient) الايجابي الوحيد كان السكر بعد أن تمت المقارنة بين المجموعتين ، حيث إن المجموعة الأولى كانت (394.36±40.82) مقارنة بالمجوعة الثانية (244.75±54.4) بقيمة عالية المعنوية ($p<0.01$) . تم قياس ضغط الدم لجميع المرضى في كلا المجموعتين وقد اخذ معدل قراءتين متتاليتين، وقد تبين إن 51% من جميع المرضى يعانون من ارتفاع في ضغط الدم . تم حساب BMI على أساس كغم/م٢ لجميع المرضى وكانت ضمن المعدلات الطبيعية.تراوحت مدة مرض السكري عند جميع المرضى بين ١٠– ٣٢ سنة .

بعد إجراء التحليل ألعاملي (Factor analysis) إحصائيا تبين إن المجموعة الأولى فسرت إن عوامل الخطورة على إحداث أمراض القلب توزعت إلى أربعة زمر ترتبط بأواصر بينها، وقد أعطت نسب مئوية لهذه العلاقة ومجموع هذه النسب 69.213%في حين كانت المجموعة الثانية قد توزعت على ثلاثة زمر فقط و مجموع النسب فيها85.897%. بنظرة سريعة إلى الزمرة الأولى من المجموعة الأولى والتي كانت 24.822% مقارنة مع الزمرة الأولى من المجموعة الثانية والتي تجمع نفس العوامل الخطرة إضافة إلى عاملي السكر والضغط كانت 42.161% مما قد تعطي تفسير لظهور تغيرات في تخطيط القلب لهذه المجموعة والتي كانت تضم المصابين بأمراض القلب .

Introduction

Diabetes mellitus (DM) can be defined as a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood, in addition to a disorder of carbohydrate, protein and fat metabolism [1].Chronic hyperglycemia in DM damages various organs and leads to a series of complications [2].Which include retinal vascular disease, renal glomerulo-sclerosis, neurological dysfunction and an increased risk of accelerated atherosclerosis. As a result of these complications, patients with diabetes have an increased probability of suffering blindness, renal failure, neuropathy, strokes, limb ischemia and heart attacks [1]. Blood vessels are the commonly affected targets and related complications are the leading causes of death in patients T2DM [2]. Thus T2DM is a cardiovascular disease; two out of three diabetic patients die of cardiovascular disease or its complications [3]. T2DM considered as CAD risk factor [4-5] at least 25% of coronary patients have sudden death or nonfatal myocardial infarction without prior symptoms [6]. CAD accounts for a large fraction of morbidity and mortality in patients with T2DM [4, 7] among cardiovascular complications, CAD has been observed most frequently, and it imposes a huge health trouble in all countries [8]. Diabetes without prior myocardial infarction and prior myocardial infarction without diabetes indicate similar risk for CAD death in men and women. However, diabetes without any prior evidence of CAD (myocardial infarction or angina pectoris or ischemic ECG changes) indicates a higher risk than prior evidence of CAD in non-diabetic subjects, especially in women [9]. Risk factors have included blood pressure, cigarette smoking, cholesterol TC, LDL-C, HDL-C, and diabetes [10]. Type 2DM is a powerful risk factor for CAD progression

[11].Conversely; plaques in asymptomatic diabetic patients were usually non-obstructive. [12].Myocardial ischemia in patients with diabetes is often asymptomatic and frequently in an advanced stage when it becomes clinically manifest [13]. The lesion may have been very severe in diabetic patients when symptoms of T2 DM developed because of the following two reasons. First, the patients may have had DM for many years before it was diagnosed because of lack of typical clinical symptoms[14] .Second, painless myocardial ischemia may have developed in a higher percentage of patients and which mask the progress of CAD[4,5].The American Diabetes Association suggested a risk factor-guided screening approach (*e.g.*, considering age, gender, hypertension, and dyslipidemia) for early detection of CAD in patients with symptomatic and asymptomatic T2DM [15] .The aim of this study was to study: First the influence of a patient's age, diabetes duration, obesity, frequency of hypertension (BP) Hyperglycemia and blood lipid profile (TC, HDL-C, LDL-C, TG) and second; matching the exciting risk factor changes in the symptomatic (abnormal ECG) and A symptomatic (normal ECG) T2DM features from their physiological point of view.

Materials and Methods

1. Materials

1.1Patients

The current study includes 100 diabetes patients, were recruited from Diabetes Unit in Marjan Teaching Hospital, 71 men and 29 women, ١٧–76 years old. Patients confirm normal ECGs were 88 (group1) while 12 from the entire patients show abnormal resting ECGs (group2) with obvious myocardial infarction, angina pectoris or ischemic ECG changes, at the baseline of examination. Patients of both sexes were included in this study.

1.2 Electrocardiograms (ECGs)

Kenz Cardio 302 three channel ECG machine was used for total patients. All the ECGs were reviewed and interpreted by a cardiology consultant[*3] based in Marjan Teaching Hospital. Patients with evidential abnormal resting ECGs were included in this study as abnormal T2DM patients (group 2).

Patients with normal ECGs (group1) occasionally have evidence of previously unrecognized MI on resting ECG, including abnormal Q-waves or deep T-wave inversions, or the presence of a left-bundle branch block (LBBB), findings usually trigger evaluation for CAD and inducible ischemia. However, non specific ST-T wave changes also are a strong predictor of inducible ischemia in asymptomatic diabetic patients [7, 16].

2. Methods

2.1 Physical examination

All patients underwent primary clinical and laboratory evaluation. Height and weight were measured, as body mass index (BMI kg/m^2) [17] was calculated. Two blood pressure (BP) determinations were made after the patient had been sitting at least 5 minutes, and the average of BP readings was included in the study. Hypertension: When BP ≥140/90mmHg (with or without medication).

2.2 Blood collection.

Venous blood samples were drawn from all patients who were fasting for at least 12 hour. The procedure done at the morning routine clinic visits then laboratory analyses were done on the blood serum.

2.3 Lipid profile

Laboratory analyses were done according to manufacturer instructions. The required volume of serum needed for each test is 30.00 µl applied onto a specific zone on the test strip, after that the strip placed on the instrument guide. The concentration for each test was calculated automatically by the Reflotrone instrument via the magnetic slip on the underside of each test strip. Serum samples were used for evaluation of serum total cholesterol TC, serum high density lipoprotein HDL-C, serum triglycerides TG and serum glucose GLU were measured by a reflectance photometer [Reflotron®Roche] with the strips of Reflotron®Roche Diagnosis Ltd. Bell Lane, Lewes, East Sussex BN71LG UK. Serum low density lipoprotein-cholesterol LDL-C was calculated by the Friedewald formula [18].

VLDL$= \frac{\text{Triglycerides}}{5}$ while LDL = {TC – (HDL + VLDL)}.

3. Statistical analysis

Data analyses were set with the SPSS programs (SPSS, Chicago) by means of Factor analysis (correlation-matrix). The results for the continuous variances were presented by initial Eigen values as their cumulative percentages. Data of nine variables include: AGE, BMI, TC, TG, HDL-C, LDL-C, glucose GLU, BP and diabetes duration (DURA) form both groups of patients were incorporated.

Variables analyses of component matrix of (group1) represent the risk factors on four categories (Tables 1A, 1B&1C) while (group2) variables descript three risk factor categories, according to their performance percent on CAD (Tables 2A, 2B & 2C).Pearson correlation coefficients were used to assess the relationship between (group1) and (group2) variables. Mean ± SD of variables from both group of patients were matched with each other (Table 3).

Results

- Factor analysis for group 1 with Normal ECGs patients in the study were designed to evaluate the most common risk factors that generate the CAD in T2DM patients, after matching the correlation between the variables. The analysis consequence reveals 4 categories (factors) of essential risk factors display the extent of serious effect proportion on CAD incidence (Table 1C).

1. Factor one: a great positive association between the variances of TC, HDL-C and LDL-C which considered as lipid profile risk factor represent 24.822%from the total variances 69.213%.
2. Factor two: the relationship between TG, glucose and duration of T2DM estimated 17.513% of variance.
3. Factor three: positive association between BMI and BP, with 15.253% variance.
4. Factor four: represent the AGE only with a variance of 11.625%.The total Cumulative percentage of the four factors = 69.213% (Table 1C).

- Factor analysis for group 2 with abnormal ECGs reveals 3 categories (factors) within their total Cumulative percentage of 85.897% where the CAD risk factors representation is more clear than that of (group1) .The loadings summarized in (Table 2C):-

1. Factor one: A positive relationship between the AGE of the patient, TC, HDL-C, LDL-C, BP, and glucose the variance % represent 42.161% from the total variances 85.897%.
2. Factor two: the variance of BMI is 19.729%.

3. Factor three: there is inverse proportion between TG value and the DURA value (duration of disease) with a variance of 15.362%. The total Cumulative percentage of the above three factors 85.897%.

Pearson correlation coefficients demonstrate negative significant difference between all variables in both groups except glucose expose an increase difference in (group1) variables P<0.01 (Table3), with 51%of all patients associated with hypertension.

Table 1 A

Group1 Communalities

	Initial	Extraction
AGE	1.000	.773
BMI	1.000	.645
DURA	1.000	.545
BP	1.000	.870
TG	1.000	.740
TC	1.000	.945
HDL-C	1.000	.631
LDL-C	1.000	.823
GLU	1.000	.259

Extraction Method: Principal Component Analysis of the Asymptomatic (normal ECG) Patients

Table 1 B Total Variance Explained distribution of group 1 Risk Factors

Component	Initial Eigen values			Extraction Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.234	24.822	24.822	2.234	24.822	24.822
2	1.576	17.513	42.335	1.576	17.513	42.335
3	1.373	15.253	57.588	1.373	15.253	57.588
4	1.046	11.625	69.213	1.046	11.625	69.213
5	.973	10.806	80.019			
6	.799	8.873	88.892			
7	.709	7.882	96.773			
8	.290	3.226	100.000			
9	9.743E-6	.000	100.000			

Extraction Method: Principal Component Analysis.

Table 1 C Group1 factors distribution

	Factors Percentage Analysis			
	1		3	4
	+TC +HDL-C +LDL-C	-TG +DURA +GLU	+BMI +BP	+AGE
Variance %69.213%	**24.822%**	**17.513%**	**15.253%**	**11.625%**

Table 2 A Group2 Communalities

	Initial	**Extraction**
AGE	1.000	.558
TC	1.000	.937
HDL-C	1.000	.755
LDL-C	1.000	.856
TG	1.000	.822
GLU	1.000	.819
BMI	1.000	.781
DURA	1.000	.640
BP	1.000	.784

Extraction Method: Principal Component Analysis of the symptomatic (abnormal ECG) Patients

Table 2 B Total Variance Explained distribution of group 2 Risk Factors

	Initial Eigen values			Extraction Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.794	42.161	42.161	3.794	42.161	42.161
2	1.776	19.729	61.890	1.776	19.729	61.890
3	1.383	15.362	77.252	1.383	15.362	77.252
4	.778	8.645	85.897			
5	.656	7.288	93.185			
6	.354	3.938	97.123			
7	.182	2.017	99.140			
8	.077	.860	100.000			
9	3.087E-17	3.430E-16	100.000			

Extraction Method: Principal Component Analysis of the symptomatic (abnormal ECG) Patients

Extraction Method: Principal Component Analysis.

Table 2 C Group 2 factors distribution

	Factors Percentage Analysis		
	1	2	3
	+AGE +TC +HDL-C +LDL-C - GLU -BP	+BMI	+TG - DURA
Variance 85.897%	**42.161%**	**19.729%**	**15.362%**

Table 3 Total Variance Explained (Mean±SD) for group 1 & group2 Patients With correlation coefficient

variable	Group 2 patients	Group 1 patients		
	Mean±SD	Mean±SD	significance	p values
AGE	55.12±9.45	57.83±10.17	negative	P=0.6602
HDL-C	36.31±11.23	43.51±19.64	negative	P =0.7338
TC	188.41±48.74	199.77±45.44	negative	P= 0.5080
TG	306.5±124.82	273.03±163,28	negative	P = 0.5031
LDL-C	90.79±39.11	101.75±37.13	negative	P = 0.4293
GLU	244.75±54.4	394.36±40.82	positive	P < 0.0001
BP	141±9.55	145.00±7.69	negative	P = 0.8088
BMI	22.442±3.27	22.513±2.424	negative	P = 0.7713
DURA	16.25±7.61	14.95652±5.20	negative	P=0.4799

Discussion

Analyses of the nine mentioned common risk factors of (group1) T2DM patients indicate that 69.213% of them had a direct effect on CAD prevalence in this cohort of patients, this explain that up till now there is about 30.787% of other risk factors not mentioned, although have more risky relationship with CAD. (Table 1C).

The summarized loadings (Table2C) of the (group2) participants indicate that the risk factors hazard within 85.897% to mark out CAD in patient's myocardial infarction or angina pectoris, LBBB, or ischemic ECG changes, but there are still about 14.11% from other causes.

Even that, the first factor variance percent, 42.16%,(Table2C) give an idea about the wide range of significant difference compared with first factor variance percent 24.822% (Table 1C) of the (group1) because of the already presented symptoms. Matching was applied on other factors of variance from (Table1C&Table2C) revels less differences.

Medical studies on T2DM patients confirmed on the traditional CAD risk factors, while our study indicate that there are more additional possible risk factors, where (group2) reveal that 30.787% out of the total sum of variances "69.213%" and (group1) about 14.11% out of the total sum of variances "85.897 %" subject of debate.

Recent studies announce possible curious risk factors, with the incidence of new-onset of T2DM with asymptomatic human Cytomegalovirus infection group was 26%, compared to control group of recipients without CMV

infection was 6%.Asymptomatic CMV infection was associated with a significantly increased risk of new-onset diabetes, [19] as well as several types of viral infections have been associated with increased risk of T2DM [20,21] also the CMV can infect pancreatic islet cells in vivo[22] and has been detected in islet cells from both type1 [23] and type2[24] diabetic Patients, considering T2DM as a powerful risk factor for CAD progression[11]. There was a correlation between diabetes, sero-positivity to CMV and age, and more significant vascular complications among patients with diabetes [25].

Peripheral tissues uptake of cholesterol from the blood through a process of LDL-C receptor-mediated endocytosis [26]. The LDL-C can pass from the blood into the arterial wall where it may be oxidized and engulfed by macrophages producing foam cells, which accumulate to form fatty streaks [27]. The present study on (group1) reveals the same result that; LDL-C correlated negatively with plasma TGs and positively with HDL-C however, an inverse correlation between the TG to HDL-C (Table1) [28]. In contrast the association between TG levels and CAD disappeared after adjusting for other risk factors. Similarly, asymptomatic men assessed for vascular risk factors, low HDL-C levels were reported to be associated with an increased risk of CAD at all levels of total cholesterol and were particularly apparent in subjects with diabetes [29]. While (group2) analyses, TGs show positive correlation (Table 2C), go with the role of TGs as a risk factor in the general population is controversial [30]. LDL-C has long been recognized as the major atherogenic lipoprotein, whereas, HDL-C is believed to protect against atherosclerosis [31]. The relationship between low levels of HDL-C and the development of CAD, the relative risk of CAD increases due to level of total cholesterol, with decreasing levels of HDL-C [32]. The various HDL-C is involved in the reverse transport of cholesterol from the peripheral tissues to the liver, thereby reducing the uptake of cholesterol by macrophages and providing a protective effect against atherosclerosis. It also has beneficial effects upon endothelial function[33,34] .Common CAD was associated with male sex, older age, lower HDL-C, low diastolic blood pressure and use of antihypertensive medication[35].

The association between diabetes mellitus and hypertension has been described in 60–65% of diabetic patients, with complications for cardiovascular risk [36, 37].On the contrast other studies on primary role of chronic hyperglycemia in the pathogenesis of the accelerated atherosclerosis in diabetic patients is still controversial [38,39]. Hypertension is an extremely common condition in DM affecting about 20% –60% of patients with diabetes. People with both DM and hypertension have approximately twice the risk of CAD. The prevalence of hypertension in patients with diabetes in the clinic-based study was 67.7% [40].

This study was comparable to 51% patients associated with hypertension, while the corresponding numbers for hypertension range between 50% and 70% [41, 42].

Conclusions

1. The sample size in this study was confined to 100 diabetic patients in one local hospital. I suggest that National population survey to include wider range of patients in different hospitals to

analyze the most common risk factors for T2DM.

2. To introduce National plan for sero-positivity tests to CMV as there was a correlation among diabetes.

References

[1] Harris, M.I. (2004). Definition and Classcification of diabetes mellitus and the criteria for diagnosis. In: LeRoith, D., Taylor, S.I., Olefsky, J.M. (Eds.), Diabetes Mellitus: A Fundamental and Clinical Text, 3rd Ed. Lippincott Williams and Wilkins, Philadelphia, PA, pp. 457–467.

[2] Heffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M (1998) Mortality from coronary heart disease in subjects with type 2 diabetes, and in non diabetic subjects with and without prior myocardial infarction. N Engl. J Med; 339:229-234.

[3] American Heart Association Circulation: (1999); 100:1134-46.

[4] Alexander CM, Landsman PB, Teutsch SM (2000) Diabetes mellitus, impaired fasting glucose, atherosclerotic risk factors, and prevalence of coronary heart disease. Am J Cardiol, 86: 897-902.

[5] Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE; (2004) Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care, 27:1954-1961.

[6] Myer burg RJ, Kessler KM, Castellanos A. (1993) sudden cardiac death: epidemiology, transient risk, and intervention assessment. Ann. Intern. Med); 119:1187–1197.

[7] Jeroen J.,Bax A. (2007) Screening for Coronary Artery Disease in Patients with Diabetes. Diabetes Care 30:2729–2736.

[8] Steiner G, (1985): Atherosclerosis, the major complication of diabetes. Adv Exp Med. Biol. 189: 277-297.

[9] Auni Juutilainen, Seppo Lehto, Tapani Rönnemaa,Kalevi Pyörälä, Markku Laakso, (2005): Type 2 Diabetes as a "Coronary Heart Disease Equivalent". Diabetes Care 28:2901–2907.

[10] Gordon T, Kannel WB. (1982): Multiple risk functions for predicting coronary heart disease: the concept, accuracy, and application. Am Heart J. 103:1031–1039.

[11] Huxley R., Barzi F, Woodward M. (2006): Excess risk of fatal coronary heart disease associated with diabetes in men & women: meta-analysis of 37 prospective cohort studies: BMJ 332:73–78.

[12] Schulte AJ, Schuijf JD, Kharagjitsingh AV, Jukema JW, Pundziute G, van der Wall EE, Bax JJ. (2008): Prevalence of coronary artery disease and plaque morphology assessed by multi-slice computed tomography coronary angiography and calcium scoring in asymptomatic patients with type2 diabetes. Heart, 94:290-295.

[13] BARI Investigators No authors listed: (2000): Seven-year outcome in the Bypass Angioplasty Revascularization Investigation by treatment and diabetic status. J Am Coll Cardiol 35:1122–1129.

[14] American Diabetes Association (1998): Screening for type 2diabetes. Diabetes Care 1998, 21: 20-22.Kaufman FR: Diabetes in children and adolescents: areas of controversy. Med Clin North Am, 82:721-739.

[15] Fasting Report: (1997): of the expert committee on the diagnosis and classcification of diabetes mellitus.Diabetes Care. 20:1183-97.
[16] Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ (2005): Identifying high risk asymptomatic diabetic patients who are candidates for screening stress single photon emission computed tomography imaging. J Am Coll Cardiol 45:43–49.
[17] Eknoyan, Garabed (2008): "Adolphe Quetelet (1796–1874)—the average man and indices of obesity". Nephrol. Dial. Transplant. 23 (1): 47–51.
[18] Friedewald WT, Levy RI, Fredrickson DS. (1972): Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem; 18:499-502.
[19] Hjelmesæth J, Sagedal1 S., · Hartmann1 A., Rollag H., Egeland T., Hagen1 M., Nordal1 K. P. , Jenssen1 T.(2004): asymptomatic cytomegalovirus infection is associated with increased risk of new-onset diabetes mellitus and impaired insulin release after renal transplantation. Diabetologia 47:1550–1556.
[20] Jaeckel E, Mann M, von Herrath M (2002): Viruses and diabetes. Ann NY Acad Sci; 958: 7–25.
[21] Fabrizi F, Lampertico P, Lunghi G, Mangano S, Aucella F,Martin P. (2005): Review article: hepatitis C virus infection and type-2 diabetes mellitus in renal diseases and transplantation. Aliment Pharmacol Ther; 21: 623–632.
[22] Jenson AB, Rosenberg HS, Notkins AL (1980): pancreatic islet-cell damage in children with fatal viral infections.Lancet 2:354–358.
[23] Pak CY, Eun HM, McArthur RG, Yoon JW (1988): Association of cytomegalovirus infection with autoimmune type 1 diabetes. Lancet 2:1–4.
[24] Lohr JM, Oldstone MB, (1990): Detection of cytomegalovirus nucleic acid sequences in pancreas in type 2 diabetes. Lancet 336:644–648.
[25] Roberts BW, Cech I. (2005): Association of type 2 diabetes mellitus and sero-prevalence for cytomegalovirus. South Med J. Jul; 98(7):686-92.
[26] Brown MS, Goldstein JL. (1983): Lipoprotein receptors in the liver: control signals for plasma cholesterol traffic. J Clin Invest; 72:743-7.
[27] Libby P. (2000): Changing concepts of atherogenesis. J Intern Med; 247:349-58.
[28] Robert B, (2000): Ratio of Triglycerides to HDL Cholesterol Is an Indicator of LDL Particle Size in Patients With Type 2 Diabetes and Normal HDL Cholesterol Levels Diabetes Care 23:1679–1685.
[29] Goldbourt U, Yaari S, Medalie JH. (1997): Isolated low HDL, cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. Arterioscler Thromb Vasc Biol; 17:107-13.
[30] Austin MA, Hokanson JE, Edwards KL. (1998): Hyper triglyceridemia as cardiovascular risk factor. Am J Cardiol.; 81:7B-12B.
[31] National Cholesterol Education Program (2001): (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of h igh blood cholesterol in adults (Adult Treatment Panel III) JAMA;285:2486–2497.

[32] Castelli WP, Garrison RJ, Wilson PWF (1986): Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA; 256:2835-8.

[33] Zeiher AM. Schachlinger V, Hohnloser SH. (1994): Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated high-density lipoprotein levels ameliorate abnormal vaso-constriction in early atherosclerosis. Circulation; 89:2525-32.

[34] Galle, J. Ochslen M, Schollmeyer P, Wanner C. (1994): Oxidized lipoproteins inhibit endothelium-dependent vasodilation. Effects of pressure and high-density lipoprotein. Hypertension; 23:556-64.

[35] Josephine Harris, Lynne Giles, Paul Finucane, Gary Andrews (2004): Prevalence of coronary heart disease and cardiovascular risk factors in a sample of older Australians: Australian Longitudinal Study of Ageing Australasian Journal on Ageing Volume 23, Issue 1, pages 25–32.

[36] Contreras F, Rivera M, Vasquez J, De la Parte MA, Velasco M. (2000): Diabetes and hypertension physiopathology and therapeutics. J Hum Hypertens; 14:S26–S31.

[37] Jonas M, Reicher-Reiss H., Boyko V., Behar S., Grossman E. (2003): Hospital and 1-year outcome after acute myocardial infarction in patients with diabetes mellitus and hypertension. J Hum. Hypertens. 17:665–670.

[38] Brownlee, M. (2001): Biochemistry and molecular cell biology of diabetic complications. Nature 414, 813–820.

[39] Semenkovich, C.F. (2004): Diabetes mellitus, lipids, and atherosclerosis. In: Le Roith,D.,Taylor, S.I.,Olefsky, J.M. (Eds.),Diabetes Mellitus: A Fundamental and Clinical Text, 3rd Edn. Lippincott Williams and Wilkins, Philadelphia,PA, 1365–1375.

[40] Arauz-Pacheco C, Parrott MA, Raskin P. (2003): American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care; 26 Suppl. 1:S80-2.

[41] Fillenbaum GG, Pieper CF, Cohen HJ, Cornoni-Huntley JC, Guralnik JM.(2000): Comorbidity of five chronic health conditions in elderly community residents: determinants and impact on mortality. J Gerontol A Biol Sci Med Sci. 55: M84–89.

[42] The sixth report of the Joint: National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med (1997): 157: 2413–46.