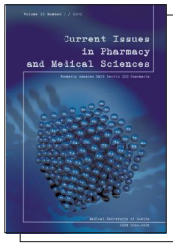

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Plasma magnesium and calcium concentrations and selected biochemical parameters in patients with type 2 diabetes mellitus

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ABSTRACT

Magnesium and calcium are known to play an important role in carbohydrate metabolism. These elements are also involved in secretion, binding, and activity of insulin. It is well-established that plasma magnesium and calcium levels in patients with diabetes mellitus are somewhat decreased. Additionally, chronic magnesium and calcium deficiency have been associated with the development of insulin resistance. Type 2 diabetes is characterized by increasing concentrations of triglycerides, total cholesterol, LDL-cholesterol and lowering of the HDL-cholesterol. Hypertriglyceridemia is often the first metabolic manifestation of insulin resistance. The purpose of this study was to determine the correlation between plasma magnesium and calcium concentrations and plasma lipids, blood glucose and glycosylated hemoglobin in type 2 diabetic patients. Magnesium and calcium concentration was determined with the colorimetric method. Lipid profile (total, HDL, LDL cholesterol, triglycerides), glycosylated hemoglobin A (HbA1c) and glucose were measured using standard methods. The plasma concentrations of glucose, HbA1c, LDL-cholesterol and triglycerides in diabetic patients were found to be significantly higher than those in the control group. The concentrations of calcium, magnesium and HDL-cholesterol were statistically lower in diabetic people in comparison to healthy individuals. In diabetic patients, a weak negative correlation was found between plasma magnesium and total cholesterol as well as between plasma magnesium and triglycerides. Positive correlations were demonstrated between plasma calcium and glycosylated hemoglobin.

Keywords: diabetes mellitus type 2, magnesium, calcium, lipid profile

INTRODUCTION

Magnesium is the fourth most abundant cation in the body that plays an important physiological role in various processes in living organisms (enzymatic reactions involving energy metabolism). Therefore, magnesium deficiency may be of clinical importance. Magnesium is a co-factor of various enzymes in carbohydrate oxidation and plays a crucial role in glucose cell membrane transporting mechanism. It is also involved in secretion, binding, and activity of insulin. It is a well-established fact that the plasma magnesium level in patients with diabetes mellitus is somewhat decreased. Magnesium deficiency and hypomagnesemia can result from a wide variety of causes, including deficient magnesium intake, gastrointestinal, and renal losses. Chronic magnesium deficiency has been associated with the development of insulin resistance [3]. The published studies confirm a relationship between hypomagnesemia and reduction in tyrosine kinase activity at the insulin receptor levels, which may result in the impaired insulin action and development of resistance to insulin [2, 12, 15]. A number of published results suggest that magnesium supplementation could be useful in treatment of diabetes and might prevent the development of its chronic complications [26, 27]. Additionally, the beneficial influence of magnesium supplementation on decrease in total and LDL cholesterol levels and on an increase in HDL cholesterol level has been reported [10, 23].

Calcium is the most abundant macroelement in the living body. Calcium and phosphorus form calcium phosphate in the bones and teeth. Calcium is essential for the normal functioning of nerves and muscles and plays a relevant role in blood coagulation (as factor IV) and in many enzymatic processes. Calcium supplementation is important in the treatment of osteoporosis, a disease that may also occur in diabetic patients, especially in old age. Diabetes mellitus is one of a large number of diseases that predispose to the development of osteoporosis [28].

Type 2 diabetes mellitus is a systemic disease characterized by a significant level of insulin resistance, varying degrees of insulin deficiency, and a wide spectrum of micro- and macro vascular, neurologic, ocular, and cardiac complications. Due to this wide diversity in manifestations of the diabetes syndrome, a phenotypic heterogeneous condition

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has been considered. However, cumulative evidence reveals that abnormal-cell Ca^{2+} homeostasis is a ubiquitous finding common to all tissues of animal and human diabetes. Consequently, abnormalities in cell Ca^{2+} metabolism may be the basic pathology in type 2 diabetes, being significant for many of its manifestations [11].

The purpose of this study was to determine the correlation between plasma magnesium and calcium concentrations and plasma lipids, blood glucose and glycosylated hemoglobin in type 2 diabetic patients.

MATERIAL AND METHODS

The study was conducted at the Department of Internal Diseases, Independent Public Health Care Unit of the Ministry of Home Affairs in Lublin. The study group included 54 patients (25 women and 29 men) suffering from type 2 diabetes mellitus. The subjects were in the age range of 41-89. The control group comprised 25 healthy non-diabetic individuals (11 women and 14 men) aged from 30 t o 60 years.

The study was approved by the Bioethics Committee at the Medical University of Lublin (Approval no. KE-0254/130/2010).

Blood samples were taken during hospitalization (in the first twenty-four hours after admission) and were transferred to the test tubes with the anticoagulant heparin. Plasma was obtained by centrifuging the whole blood samples at 3.500 rpm for 15 minutes.

Magnesium concentration was determined with the colorimetric method using xylidyl blue, which reacts with magnesium in alkaline solution to form a purple-colored complex compound. Calcium concentration was determined colorimetrically using o-cresolphtalein, which reacts with calcium in alkaline solution to form a violet-colored complex compound. The color intensity of the formed complexes is proportional to the magnesium and calcium concentrations in test samples. The Cormay diagnostic kits (Liquick Cor-MG 60 and Liquick Cor-CALCIUM 60) for magnesium and calcium determinations were used. A single beam Genesis spectrophotometer with a wavelength 520 nm and 575 nm was used to determine magnesium and calcium concentrations, respectively.

Lipid profile (total, HDL, LDL cholesterol, triglycerides), glycosylated hemoglobin A (HbA1c) and glucose concentration were measured using standard methods in Clinical Pathology Branch of the Ministry of Interior and Administration Hospital in Lublin. The lipid profile was measured with the chemical analyzer Roche Integra 400. The glycosylated hemoglobin A was determined using turbidimetric inhibition immunoassay (TINIA) and chemical analyzer Roche Cobas Integra Plus.

Statistical analysis

All statistical analyses were performed using STATISTICA program (version 10.0). Data were expressed as an arithmetic mean ± SD (standard deviation), a median and maximum and minimum range with respect to their distribution. The normality of data distribution was verified using the Shapiro-Wilk test. Differences between groups were analyzed with Mann-Whitney U (for non-normally distributed variables) or Student's *t* (for normally distributed variables) tests. Correlations between measured parameters were determined by the Pearson's correlation coefficient or Spearman's rho as a nonparametric correlation coefficient. For all analyses, p values less than 0.05 (p.05) were considered as significant.

RESULTS

Baseline characteristics of the diabetic and control groups are presented in Table 1.

In the diabetic patients group, the mean plasma magnesium was 1.07 mg/dl and the mean plasma calcium – 2.38 mg/dl. The mean concentration of plasma triglycerides was 133.2 mg/dl, total cholesterol – 185.5 mg/dl, LDL-cholesterol – 104.0 mg/dl, HDL-cholesterol – 50.5 mg/dl. The mean blood glucose concentration was 146.5 mg/dl and the hemoglobin A1c value was 7.69%.

In the control group, the mean plasma magnesium and calcium concentrations were 1.29 and 2.61 mmol/l, respectively. The mean concentrations of plasma triglycerides were 62.7 mg/dl, total cholesterol – 167.5 mg/dl, LDL-cholesterol – 88.0 mg/dl, HDL-cholesterol – 66.0 mg/dl. The mean blood glucose concentration was 84.5 mg/dl and the hemoglobin A1c value was 5.40%.

As presented in Table 1, the plasma levels of glucose, HbA1c, LDL-cholesterol and triglycerides in diabetic patients were found to be significantly higher than the ones in the control group. Moreover, the total cholesterol concentration was also higher in diabetic patients in comparison to control group, but these differences were not statistically significant. However, calcium, magnesium and HDL-cholesterol concentrations were statistically lower in the diabetic group compared to healthy people.

As shown in Table 2, the plasma glucose, HbA1c and triglyceride levels in the diabetic women and men were significantly higher than in control women and men, respectively. In contrast, the concentration of calcium was statistically lower in diabetic group than in control group – among both women and men. In addition, LDL-cholesterol value was significantly higher in diabetic women group than that in control women group. Magnesium concentration was significantly lower in diabetic men group in comparison to control men group.

As depicted in Table 2, in patients with diabetes no significant differences in plasma glucose, HbA1c, total cholesterol, LDL-cholesterol, triglycerides, magnesium and calcium levels between men and women were found. However, a significant difference in plasma HDL (p=0.039) between both individuals was noticed. In the control group no significant differences in plasma glucose, HbA1c, total, LDL- and HDL-cholesterol, triglycerides, magnesium and calcium levels between men and women, were observed.

In this study, in the group of diabetic patients a weak negative correlation between plasma magnesium and total

Table 1. Mean, median, minimum, maximum and standard deviation values in diabetic and control group

Parameters	Diabetic group (n = 54)					Control group (n = 25)					Statistical analysis – p value
	Mean	Median	Minimum	Maximum	SD	Mean	Median	Minimum	Maximum	SD	
Glucose [mg/dl]	159.0	146.5	89.0	312.0	46.9	84.5	83.8	67.8	99.2	8.6	**0.000001**
HbA1c [%]	7.70	7.69	6.10	12.10	1.06	5.27	5.40	4.10	5.80	0.42	**0.000001**
T-CHOL [mg/dl]	185.5	178.0	48.0	296.0	47.4	167.5	166.0	121.0	200.0	21.9	0.074672
HDL [mg/dl]	49.5	50.5	21.0	95.0	14.2	65.8	66.0	36.0	90.8	14.8	**0.000022**
LDL [mg/dl]	104.0	99.0	32.0	193.0	34.1	88.0	86.0	58.0	127.0	18.4	**0.031749**
TRIGL [mg/dl]	159.7	133.2	49.0	458.0	87.6	71.9	62.7	38.7	132.0	25.4	**0.000001**
Mg [mmol/l]	1.07	1.07	0.46	1.44	0.25	1.27	1.29	0.95	1.47	0.15	**0.001045**
Ca [mmol/l]	2.38	2.37	1.99	2.94	0.25	2.61	2.63	2.20	2.99	0.20	**0.000139**

HbA1c – glycosylated hemoglobin, T-CHOL – total cholesterol, TRIGL – triglicerydes, SD – standard deviation

Table 2. Mean, median, minimum, maximum and standard deviation values in women and men of diabetic and control groups

Parameters	Sex	Diabetic group (25 F, 29 M)					Statist. anal. (p) F/M	Control group (11 F, 14 M)					Statist. anal. (p) F/M	Statist. anal. (p) D/C
		Mean	Median	Minimum	Maximum	SD		Mean	Median	Minimum	Maximum	SD		
Glucose	F	154.8	152.0	89.0	308.0	41.1	0.95	83.9	83.6	71.6	99.2	9.5	0.76	**0.000004**
[mg/dl]	M	162.6	144.0	117.0	312.0	51.9		85.0	85.0	67.8	98.2	8.2		**0.000002**
HbA1c	F	7.77	7.69	6.10	12.10	1.23	0.81	5.28	5.30	4.30	5.70	0.42	0.72	**0.000002**
[%]	M	7.62	7.69	6.10	9.70	0.90		5.27	5.40	4.10	5.80	0.53		**0.000001**
T-CHOL	F	195.2	179.0	48.00	296.0	55.7	0.16	164.4	163.0	121.0	197.0	21.9	0.54	0.086697
[mg/dl]	M	177.1	174.0	94.0	255.0	37.8		169.9	178.0	125.0	200.0	22.4		0.517002
HDL	F	52.0	54.6	21.0	80.0	12.9	**0.039**	64.1	61.6	41.3	90.8	17.8	0.52	**0.028024**
[mg/dl]	M	47.4	46.0	27.0	95.0	15.0		67.2	67.2	36.0	87.8	12.4		**0.000132**
LDL	F	109.8	99.0	69.0	193.0	31.5	0.24	87.6	86.0	58.0	127.0	20.4	0.92	**0.048308**
[mg/dl]	M	98.9	99.0	32.0	186.0	36.0		88.4	87.0	67.0	112.0	17.4		0.218285
TRIGL	F	144.0	133.2	78.0	319.0	58.4	0.22	63.2	62.2	38.7	109.4	20.2	0.19	**0.000012**
[mg/dl]	M	173.2	133.2	49.0	458.0	105.8		78.7	80.2	44.0	132.0	27.6		**0.000233**
Mg	F	1.08	1.07	0.64	1.43	0.23	0.77	1.21	1.28	0.95	1.42	0.18	0.19	0.126974
[mmol/l]	M	1.06	1.07	0.46	1.44	0.27		1.31	1.34	1.10	1.47	0.10		**0.001872**
Ca	F	2.34	2.36	2.02	2.82	0.22	0.24	2.59	2.63	2.20	2.89	0.23	0.59	**0.004896**
[mmol/l]	M	2.42	2.38	1.99	2.94	0.27		2.63	2.62	2.30	2.99	0.18		**0.010955**

HbA1c – glycosylated hemoglobin, T-CHOL – total cholesterol, TRIGL - triglycerides, SD – standard deviation, F – female, M – male, D –diabetic group, C – control group

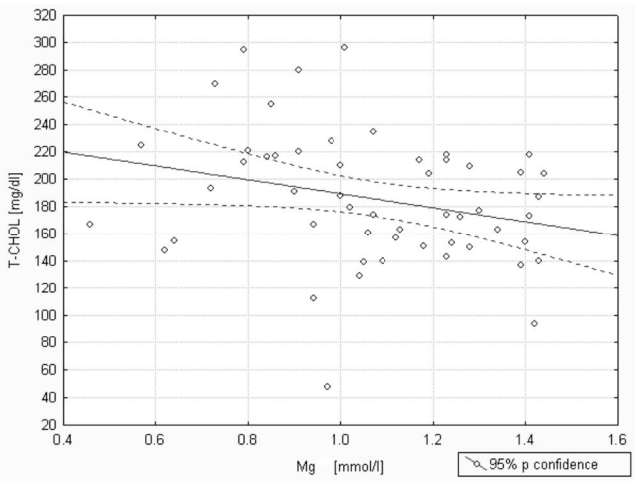

Figure 1. Weak negative correlation between plasma magnesium and total cholesterol (r=-0.27, p=0.05) in diabetic group

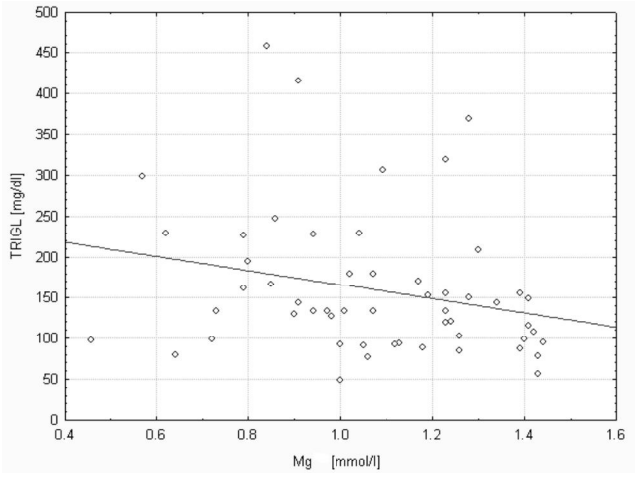

Figure 2. Weak negative correlation between plasma magnesium and triglycerides (R_s=-0.28, p=0,03) in diabetic group

cholesterol (r=-0.27, p=0.05) (Figure 1) and between plasma magnesium and triglycerides (R_s=-0.28, p=0.03) (Figure 2) were found. However, no significant correlations between plasma magnesium and plasma glucose, HbA1c, HDL, LDL and calcium concentration were observed.

Moreover, the conducted examination showed positive correlations between plasma calcium and glycosylated hemoglobin (R_s=0.35, p=0.008) (Figure 3) in diabetic group. No significant correlations between calcium concentration and other tested parameters like plasma glucose, total cholesterol, HDL, LDL and triglycerides were noticed. Additionally, weak positive correlations between plasma triglycerides and HbA1c (r_s=0.33, p=0.01) and between plasma triglycerides and total cholesterol (r_s=0.27, p=0.04) were found.

In the control group, no correlations between the tested parameters were observed.

DISCUSSION

Magnesium is known to play an important role in carbohydrate metabolism, and its imbalance has been implicated in diabetes mellitus consequently. In our study, a lower level of magnesium in diabetes patients in comparison to healthy individuals was observed. Abou-Seif and Youssef [1] ob-

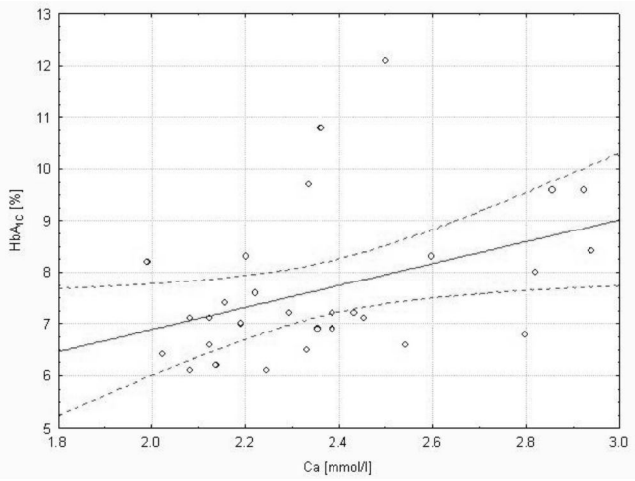

Figure 3. Positive correlation between calcium and HbA1c values in diabetic group

served lower plasma magnesium concentrations in patients with type 2 diabetes mellitus and reduced antioxidative protection in type 1 and type 2 diabetes mellitus. Low magnesium levels may be supposed also to lead to the reduction of protective enzymes against oxidative stress [15]. Decreases in both of these parameters can be the factor increasing the risk of chronic diabetes complications. The vascular complications mostly associated with the deficiency of magnesium are: ischemic heart disease, atherosclerosis, hypertension, metabolic syndrome, hypertriglyceridemia and hypercholesterolemia [26]. The relation between the two last complications and decreased magnesium concentration was also recorded in our study – the plasma concentrations of total cholesterol, LDL cholesterol and triglycerides in diabetic patients were found to be higher than the ones in control group. Moreover, according to Habib *et al.* [6], there is a significant positive correlation between plasma lipoprotein, total cholesterol and LDL-cholesterol in diabetic patients.

Higher concentrations of plasma total cholesterol, LDL-cholesterol, triglycerides and lower concentrations of HDL-cholesterol in the diabetic patients are not surprising. Type 2 diabetes is characterized by increasing of triglycerides and lowering of HDL fraction of cholesterol concentrations. In diabetes mellitus these changes are triggered by the phenotype changes of HDL and LDL fractions of lipoproteins, which alter the composition of these lipoproteins – very low-density lipoproteins (VLDL) are produced and therefore the concentration of triglycerides increases. This process accelerates the catabolism of these lipoproteins and causes impairment of the transport of maneuverable cholesterol from the tissues [22].

Furthermore, studies conducted on experimental animals have shown that lipoproteins modulate the function and survival of insulin secreting cells. Purified human VLDL and LDL participles reduce insulin mRNA levels and β-cell proliferation, while there is a dose-dependent increase in the rate of apoptosis [24]. The inhibitory effects of LDL on insulin secretion and β-cell proliferation have also been shown in primary human islets [25].

In type 2 diabetic patients with essential hypertension, reduced cytosolic free magnesium concentrations were observed, compared to normotensive or non-diabetic individuals [26]. According to the hypothesis suggested by Paolisso and Barbagallo [18], low availability of intracellular magnesium diminishes the tyrosine kinase activity and increases the vascular construction mediated by calcium, hindering the relaxation of cardiac and smooth muscles; and thus interfering the usage of the cellular glucose. Such a mechanism contributes to increased blood pressure and peripheral insulin resistance, suggesting secondary etiological factors of hypertension and type 2 diabetes. Moreover, this mechanism may also result in impairment of insulin receptor levels and development of insulin resistance [15].

Some studies have suggested that adequate magnesium intake reduces the risk of development of type 2 diabetes; there are still contradictions with respect to the role of low magnesium intake as a predictor factor for this disease [27]. The importance of magnesium for individuals with diabetes can be explained on the basis of maintenance of glucose homeostasis along with activation of factors involved in sensitivity of tissues to insulin, the receptors of which are phosphorylated only in the presence of Mg^{2+}ATP. Some studies have shown that the magnesium intake by patients with diabetes is often below the recommended levels. Additionally, there is evidence that the magnesium status of patients with diabetes tends to alter, and that low body concentrations of this macroelement may influence the evolution of the disease and generate its further complications [27].

Various data suggest that magnesium supplementation could be useful in the treatment of diabetes and prevention of its chronic complications. The study carried out by Mooren *et al.* [14] proved significant evidence that magnesium supplementation ameliorated insulin resistance. Moreover, glucose handling seemed to be improved as the fasting plasma glucose significantly decreased after intervention. Interestingly, in this study, insulin resistance improved in spite of normal plasma magnesium concentrations. The authors suggested that magnesium in excess might act as a natural insulin sensitizer even under conditions of a well-balanced status of this bioelement.

The role of calcium in carbohydrate metabolism is also important. Our investigation demonstrated that concentrations of calcium were statistically lower in diabetic patients in comparison to healthy individuals. Moreover, positive correlations between plasma calcium and glycosylated hemoglobin in diabetic group were observed. It is commonly known that in people without diabetes, hypocalcaemia is associated with impairment of insulin release [19].

Glucose intolerance and type 2 diabetes mellitus are often associated with defects in pancreatic β-cell function, insulin sensitivity, and systemic inflammation [8]. There is evidence that calcium affects these mechanisms. Defects in cell Ca^{2+} regulation may be of significance for impaired insulin secretion, and the impaired insulin action observed in type 2 diabetes, and may play an important role in the associated

vascular complications, such as atherosclerosis and hypertension, as well as in pathogenesis of some of microvascular, ocular, and neurologic complications. Therefore, changes in cell Ca^{2+} homeostasis could be a common pathology linking most of diverse features of type 2 diabetes syndrome [11].

Calcium is essential for insulin-mediated intracellular processes in insulin-dependent tissues such as skeletal muscle and adipose tissue [17, 29], with a very narrow range of calcium concentration needed for optimal insulin-mediated functions. Changes in calcium concentration in primary insulin target tissues may contribute to peripheral insulin resistance via impaired insulin signal transduction [19], leading to decreased glucose transporter-4 (GLUT-4) activity. Moreover, changes in calcium concentration modulate adipocyte metabolism, which may promote triglyceride accumulation via increased de novo lipogenesis and inability to suppress insulin-mediated lipolysis leading to fat accumulation [13, 30]. Patients with type 2 diabetes mellitus exhibit impaired cellular calcium homeostasis including defects in the skeletal muscles, adipocytes and liver [19].

It is currently recognized that type 2 diabetes mellitus is associated with systemic inflammation [5, 8, 21]. Systemic inflammation has been linked primarily to insulin resistance, but increased cytokine levels may also play a role in β-cell dysfunction by triggering β-cell apoptosis. There are very limited and conflicting data from human studies analyzing the relationship between calcium status and systemic inflammation in relation to type 2 diabetes mellitus [4, 19, 20].

Additionally, lower plasma calcium concentrations in diabetic patients could be connected with osteoporosis. Diabetes mellitus and osteoporosis are two frequent medical conditions with an increasing prevalence in the aging population. A survey of a prospective cohort of postmenopausal women in the Iowa Women's Health Study [16] revealed that women with type 2 diabetes mellitus had a 1.7-fold higher risk of hip fractures compared to women without type 2 diabetes mellitus. Long-standing type 2 diabetes mellitus was suggested to predispose to a higher incidence of falls, thus increasing the likelihood of suffering fractures, despite higher average bone mineral density reported in these patients [7].

Glycosylated hemoglobin results from post translation changes in hemoglobin molecule, and their levels correlate well with glycemic levels over previous six or ten weeks. Glycosylation of hemoglobin takes place under physiological condition by a reaction between glucose and N-terminal valine of β-chain of hemoglobin molecules [9]. We noticed statistically higher level of HbA1c in diabetic patients group when compared to control group. It is worth noting that higher levels of this parameter indicate risk for development of microangiopathy in diabetic. HbA1C has special affinity for oxygen thereby causes tissue anoxia and plays a role in patomechanism of micro- and macroangiopathy [9]. Thus the measurement of glycosylated hemoglobin not only shows promise of being a successful approach to the monitoring of diabetic patients but also provides a conceptual framework for the pathogenesis of secondary sequences of diabetes.

CONCLUSION

1. The study demonstrated elevated concentrations of plasma glucose, glycosylated hemoglobin, triglycerides, total cholesterol, LDL-cholesterol and diminished concentrations of HDL-cholesterol, plasma magnesium and calcium compared to control group.
2. The plasma glucose, HbA1c and triglyceride levels in diabetic women and men were significantly higher than in control women and men. The concentration of calcium was statistically lower in diabetic group than in control group – both among women and men.
3. A significant difference in plasma HDL between men and women in diabetic group was observed.
4. The study demonstrated negative correlation between plasma magnesium and total cholesterol and between plasma magnesium and triglycerides in diabetic group.
5. The study findings showed positive correlations between plasma calcium and glycosylated hemoglobin in diabetic group.

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