Original article

Levels of LDL Cholesterol, Triglyceride and Urate in Patients With Type 2 Diabetes Mellitus

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Abstract

Aim: The study aimed to examine LDL cholesterol, triglyceride and urate levels in patients of both sexes with type 2 diabetes mellitus (DM2T) in family medicine offices and to examine whether there is a difference in these parameters between obese patients and patients with normal body weight with DM2T, and between patients with and without manifest cardiovascular diseases.

Participants and methods: The study was organized as a cross-sectional study. It included 136 participants of both sexes diagnosed with DM2T, who were divided into groups of patients with or without adiposity and into groups of patients with or without experience of cardiovascular event. General and demographic data were collected, as well as data on experiencing cardiovascular events and levels of LDL cholesterol, triglycerides and urates.

Results: The average LDL cholesterol level was 2.93 mmol/L, the average triglyceride level was 1.65 mmol/L and the average urate level was 326.36 µmol/L. Only 12.5% of participants reached target LDL cholesterol levels, while levels of triglycerides and urates were within recommended limits. 24.3% of participants had experienced cardiovascular events and 39.7% of participants were obese. There was no significant difference in levels of LDL cholesterol, triglycerides and urates in participants who had experienced a cardiovascular event and those who had not. There was a significantly higher concentration of triglycerides in obese patients than in patients with normal body weight ($p = 0.005$).

Conclusion: In addition to regulation of glycaemia in patients with DM2T, statin doses should be increased in order to reach the target levels of LDL cholesterol. When it comes to obese patients, education courses on physical activity and diet should be conducted more often and, if necessary, fibrates should be included in therapy in order to reduce additional cardiovascular risks.

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Introduction

Diabetes mellitus is a chronic and progressive disease. Nowadays it is one of the most important public health problems and for many years it has been among the top ten causes of death in the Republic of Croatia (1). The International Diabetes Federation estimates that more than 420 million people worldwide suffer from diabetes, and it is predicted that in the next 25 years, this number will reach 630 million (2). The number has increased every year in the Republic of Croatia and persons diagnosed with diabetes, currently counting over 260,000 people, are considered to be only half of the actual total number of patients (3). Despite the good-quality and affordable healthcare in the Republic of Croatia, diabetes is often detected or treatment starts in an advanced stage, which affects both the quality and the cost of diabetes treatment. Croatian Health Insurance Fund data for 2016 showed that the total cost of treating diabetes in the Republic of Croatia amounted to HRK 4.6 billion, accounting for almost 20% of the total Croatian Health Insurance Fund budget (4).

Pathophysiology of diabetes is complex and it includes the interaction of genetic and environmental factors (1). Modern, sedentary lifestyle and excess energy intake undoubtedly lead to a state of overweight and obesity, where, due to the increase of visceral fat tissue, insulin resistance occurs; this is, in addition to beta-cell dysfunction and impaired insulin secretion, a major pathophysiological disorder for development of diabetes, along with many other conditions, such as increased gluconeogenesis, increased glucagon secretion in pancreatic α-cells, decreased incretin effect, increased lipolysis, increased renal glucose reabsorption and neurotransmitter disorder (1, 5). For this reason, educating patients on physical activity and diet planning plays an important role in the long-term regulation of diabetes (6).
It is estimated that 75% of diabetic patients suffer from at least one other associated disease. Cardiovascular diseases occur 15 years earlier in such patients, being the leading cause of mortality (7). Diabetic patients have a higher prevalence of coronary heart disease, a more severe degree of coronary ischemia and 2 to 3 times more frequent myocardial infarction with a worse prognosis (8). Factors identified for the development of atherosclerosis, which we can affect, are hyperlipoproteinemia, hyperglycaemia, hypertension, hyperhomocysteinemia, smoking and obesity. It has been shown that by controlling these factors, cardiovascular mortality is significantly reduced, even in the case of patients with type 2 diabetes (9, 10).
According to the cardiovascular risks table referred to in the 2019 guidelines, patients with type 2 diabetes belong to the group of moderate cardiovascular risk if they are under 50 years of age and the disease itself has been present for less than 10 years without additional risk factors. In case of type 2 diabetes lasting for 10 years or longer with the presence of a risk factor or type 2 diabetes without damage to the target organs, cardiovascular risk was assessed as high. Diabetic patients who suffered damage to target organs (e.g., proteinuria or severe chronic kidney disease with glomerular filtration rate – eGFR < 30 mL/min/1.73 m2, retinopathy or neuropathy) or had at least 3 risk factors belong to the group of patients with very high cardiovascular risk.

The target LDL cholesterol level for the group of patients with very high cardiovascular risk is < 1.4 mmol/L and a 50% or greater decrease of the initial level, while target LDL cholesterol levels at the time when this research was conducted, according to the 2016 guidelines, amounted to < 1.8 mmol/L or a 50% or greater decrease of the initial level of LDL cholesterol (11). Despite the available therapy, diabetic patients are still at additional cardiovascular risk regarding the rapid development of atherosclerosis. Although the prevalence of increased levels of LDL cholesterol is lower each day, the prevalence of high levels of triglycerides and low levels of HDL cholesterol has doubled in recent years, which may be connected to the increasing number of obese people (metabolic syndrome). Therefore, body mass regulation and pharmacotherapy for lowering triglyceride levels and increasing HDL cholesterol levels play an important role (12).

The objectives of this research were to determine the average concentrations of LDL cholesterol, triglycerides and urates in patients of both sexes with type 2 diabetes in family medicine offices of the Healthcare Centre Osijek and to examine whether there is a difference in these parameters between obese patients and patients with normal body weight, as well as between patients with and without manifest cardiovascular disease. The research also examined whether obese diabetic patients and diabetic patients with manifest cardiovascular disease would reach target levels of LDL cholesterol, triglycerides and urates.

Participants and methods

The research was organized as cross-sectional, with data collected at a defined time, and it was conducted in two family medicine offices in the Healthcare Centre Osijek. Before the research, participants were provided with detailed information on the planned research and they read and signed the informed consent document. Participants were over 18 years of age, of both sexes, diagnosed with type 2 diabetes. A total of 136 participants were included in the research, of which 55 were men and 81 were women, with an average age of 69.33 (SD = 10.87). The above-mentioned selection of participants and the size of the sample ensured the representativeness of the sample and objective results. Participants were anonymised, with each participant being assigned a unique code, i.e. a number. For the purpose of the research, the participants were further divided into groups of patients who have experienced a cardiovascular event and those who have not, as well as into groups of obese patients and patients with normal body weight. The research was approved by the Ethics Committee of the Healthcare Centre Osijek and the Ethics Committee of the Faculty of Medicine Osijek of the Josip Juraj Strossmayer University of Osijek.

When visiting the family medicine office, after the participants had been informed of the contents of the informed consent document and after they had signed it, which was a prerequisite for participating in the research, the following data were collected: demographic data (sex, age), data on duration of diabetes, data on body height and weight, and whether the occurrence of a cardiovascular event (acute myocardial infarction, angina pectoris, stroke, transient ischemic attack) was documented in the available medical records. Data on the existence of diabetes-related complications (diabetic retinopathy, nephropathy and macrovascular complications) were also collected from the medical records. Data on concentrations of LDL cholesterol, triglycerides, urates, plasma glucose and HbA1c were collected from laboratory findings.

LDL cholesterol, triglyceride and urate concentrations were measured using the Beckman Coulter Olympus AU680 chemistry analyser in accordance with the manufacturer's instructions. Triglyceride concentration was measured photometrically, using glycerol-phosphate-oxidase (GPO-PAP), LDL cholesterol concentration was measured using a homogeneous enzymatic assay, and urate concentration was determined by photometry using the UV uricase method. Concentrations of glycated haemoglobin were determined using the turbidimetric immunoinhibition method, whereby the sample for analysis was whole blood with EDTA as an anticoagulant.

Statistical analysis

Categorical data were presented as absolute and relative frequencies. Numerical data were described as the arithmetic mean and standard deviation in case of normal distribution and as the median and interquartile range in other cases. Differences between categorical variables were tested using the $\chi 2$ test and Fisher's exact test, where necessary. Normality of distribution of numerical variables between two independent groups was tested using Student's t-test and Mann-Whitney U test in case of deviation from normal distribution. Correlation between the variables was expressed as Pearson's correlation coefficient in cases where variables follow a normal distribution or Spearman's correlation coefficient in cases where variables do not follow a normal distribution. All P values are two-tailed. The level of statistical significance was set at $\alpha = 0.05$. The MedCalc Statistical Software version 18.11.3 was used for statistical analysis.

Results

The research included 136 participants, of which 81 were women and 55 were men. The average duration of diabetes in patients was 9 (4-14) years. The mean level of fasting plasma glucose test was 8.43 ± 2.99 mmol/L and the mean level of HbA1C was 7.15% with interquartile range of 6.70-8.30%. 97 (71.3%) participants experienced diabetes-related complications and the most common complication was diabetic retinopathy, with 16.2% of participants experiencing it. 15.4% of participants had an acute myocardial infarction and 12.5% of participants had a stroke or a transient ischemic attack. 14.0% of participants experienced two or more complications. 24.3% of participants were diagnosed with cardiovascular diseases, and 39.7% were obese (BMI > 30 kg/m2). There was no statistically significant difference with regard to adiposity (chi-square test, p = 0.084) and incidence of cardiovascular diseases (chi-square test, p = 0.060) between men and women.

In the highest number of participants, 64%, LDL cholesterol levels were > 2.5 mmol/L and only 12.5% of participants reached the recommended target levels of LDL cholesterol (< 1.8 mmol/L). Mean triglyceride and urate levels were within the recommended levels and no statistically significant difference was found between men and women (Table 1)..

Table 1. Mean levels of LDL cholesterol, urates and triglycerides in patients with type 2 diabetes

	Level
LDL cholesterol (mmol/L)	2.93 ± 1.02
Triglycerides (mmol/L)	1.65 (1.25 – 2.40)
Urates (mmol/L)	326.36 ± 98.55

The difference in levels of LDL cholesterol, triglycerides and urates was also examined between the group of participants who have experienced a cardiovascular event and the group of participants who have not experienced it, and no statistically significant difference was found. Target LDL cholesterol levels were not reached in either group, target triglyceride levels were reached in the group of participants who have not experienced a cardiovascular event, and target urate levels were reached in both groups (Table 2).

Table 2. Mean levels of LDL cholesterol, triglycerides and urates in patients with type 2 diabetes – comparison of the group of participants who have experienced a cardiovascular event and the group of participants who have not

	Experienced CV event (N = 33)	Not experienced CV event (N = 103)	p
LDL cholesterol (mmol/L)	2.88 ± 1,06	2.95 ± 1.01	0.733*
Triglycerides (mmol/L)	1.80 (1.30 – 2.45)	1.60 (1.20 – 2.40)	0.650**
Urates (mmol/L)	332.79 ± 11.02	324.28 ± 9.51	0.668*

*Student's t-test; **Mann-Whitney U test

Finally, our research examined the difference in LDL cholesterol, triglyceride and urate levels in obese patients and patients with normal body weight. The mean triglyceride level was significantly higher in the group of obese patients than in the group of patients with normal body weight (Mann-Whitney U test; p = 0.005), while the tested difference in LDL

cholesterol and urate levels was not significant. Participants with normal body weight did not reach target LDL cholesterol levels, while obese participants did not reach target LDL cholesterol, triglyceride or urate levels (Table 3).

Table 3. Mean levels of LDL cholesterol, triglycerides and urates in patients with type 2 diabetes – comparison of obese participants and participants with normal body weight

	Obese (N = 54)	Normal body weight (N = 82)	p
LDL cholesterol (mmol/L)	3.05 ± 0.92	2.86 ± 1.08	0.325*
Triglycerides (mmol/L)	2.20 (1.48 – 2.75)	1.50 (1.10 – 2.08)	0.005**
Urates (mmol/L)	342.13 ± 13.85	316.48 ± 10.64	0.141*

*Student's t-test; **Mann-Whitney U test

Discussion

One of the biggest challenges in family medicine is regular and in-depth monitoring of a chronic patient's medical condition, especially of patients with type 2 diabetes and patients with multimorbidities, as well as continuous education on the importance of maintaining normal glucose levels, physical activity and diet planning in order to prevent the development of microvascular and macrovascular complications, which increase patient mortality as well as reduce the quality of life.

Factors which often complicate regular monitoring and counselling of chronic patients, including diabetic patients, in family medicine offices are the increasing number of patients visiting out-patient clinics per day and their lack of response due to insufficient levels of education. All of the above shows that providing healthcare for patients with type 2 diabetes is a difficult task and a special challenge, as well as that treatment priorities should be set together with the patients, bearing in mind the professional guidelines, associated diseases, existing therapy and the patients' social status.

Guidelines of the American Diabetes Society (ADA) and the European Association for the Study of Diabetes (EASD) issued in October 2018 recommend HbA1c levels < 7% for most patients, ≤ 6.5% for younger patients and patients without comorbidities, and ≤ 7.5% for older patients with longer duration of disease and comorbidities (13). Mean HbA1c levels in our research were 7.15%, which corresponds to the guidelines' recommendations, given that our participants were older patients with multimorbidities whose average age was 69.33 ± 10.87. In a similar large-scale study conducted in family medicine offices in the Republic of Croatia, HbA1c levels were 7.6% on average, which is slightly above the recommended levels (14).

The most common complication in participants is diabetic retinopathy, which 16.2% of participants had been diagnosed with; this can be compared to the results obtained in Croatian and worldwide studies, with values ranging between 18 and 20% (14,15).

The average urate and triglyceride levels in participants were within the reference values irrespective of sex. Only 12.5% of participants reached target LDL cholesterol levels, and LDL cholesterol levels of 64% of participants were over 2.5 mmol/L, which also corresponds to results obtained in large-scale studies conducted at the level of primary healthcare worldwide, where LDL cholesterol levels of 60 to 65% of participants amounted to 2.6 mmol/L and over (16).
The average triglyceride level was 1.65 (1.25 – 2.40) mmol/L, which is a better result than the one obtained in other studies conducted in family medicine offices in the Republic of Croatia. Research conducted by Naqvi Syeda et al. in 2017 showed a strong correlation between high triglyceride levels and high HbA1c levels in diabetic patients (r = 0.278, p value < 0.0001). Given the results, the use of HbA1c levels as

markers for dyslipidaemia, especially for hypertriglyceridemia, has been proposed in order to minimize cardiovascular risks in diabetic patients through timely administration of adequate therapy (14,17).

Average urate levels in our research were also within the reference values, 318.97 ± 11.11 μmol/L for women and 337.44 ± 13.09 μmol/L for men. Urates or uric acid are organic substances produced as a final product of purine metabolism. Hyperuricemia is a condition in which plasma urate levels exceed recommended levels and it is frequently found in persons with congestive heart failure. Given that persons with type 2 diabetes are at increased risk for the development of cardiovascular diseases, and ultimately heart failure, it is considered that correction of hyperuricemia is very important for them. Many studies examined the correlation between increased urate concentration and the development of insulin resistance and diabetes, dyslipidaemia, arterial hypertension and abdominal obesity, but the results were contradictory (18, 19, 20).

The average body mass index of our participants was 29.48 ± 5.64 kg/m2, with 39.7% of participants having a body mass index > 30 kg/m2, which classifies them as obese. Tested differences in obesity between men and women were not significant (chi-square test, p = 0.084). In Croatia, approximately 25.3% of men and 34.1% of women are considered obese, which is consistent with the results of our research. Nowadays, obesity is almost the biggest health problem as it has become a pandemic, and in pathophysiological terms it is closely linked to the onset of many chronic diseases, including diabetes and cardiovascular diseases. There are many causes of obesity and the healthcare system's attempt to stop this pandemic has not produced satisfactory results so far. Programs in many countries are focused mainly on therapeutic rather than preventive approach, since prevention requires serious long-term investments with generally uncertain results. Prevention programs should focus on children and young people in order for them to adopt healthy habits and behaviour patterns in a timely manner, which, in the long run, would certainly contribute to reducing obesity in adults, and thus to decreasing its negative effects on population health (21). The research compared LDL cholesterol, triglyceride and urate levels between the groups of obese diabetic patients and diabetic patients with normal body weight. As expected, LDL cholesterol, triglyceride and urate levels were higher in the group of obese patients, but a statistically significant difference between the two groups was only shown with regard to triglyceride levels (Mann-Whitney U test, p = 0.005). The group of obese patients did not reach the target levels of any of the examined parameters (LDL cholesterol, triglycerides and urates), while the group of patients with normal body weight reached the target levels of urate and triglycerides, confirming the correlation between adiposity and these parameters.

Cardiovascular diseases are considered to be a major cause of mortality in patients with type 2 diabetes, but also in the general population. Many studies have demonstrated the existence of equal mortality risk caused by coronary diseases in patients with type 2 diabetes who have not experienced a cardiovascular event and patients who are not suffering from type 2 diabetes, but who have experienced a cardiovascular event (22). Diabetic patients who had an acute myocardial infarction are 43% more likely to experience a recurrent cardiovascular event than diabetic patients who have never experienced a cardiovascular event (23). Out of the total number of our participants, 24.3% of them have experienced a cardiovascular event and no statistical difference was found between men and women (chi-square test, p = 0.060), which is very likely connected to the high average age of participants, i.e. menopause in women, which makes cardiovascular risk equal for both sexes.

A large prospective Korean study examined the correlation between LDL cholesterol levels and the onset of cardiovascular events in patients with type 2 diabetes who had not experienced a cardiovascular event. The patients were monitored for 7 years. The average LDL cholesterol levels in participants were 2.94

mmol/L, which is similar to the results obtained in our research. The patients were further divided into groups of patients who were taking statin therapy and those who were not. There was a statistically significant increased risk of cardiovascular event occurrence in the group of patients who were not taking statin therapy, while LDL cholesterol levels were > 3.37 mmol/L and > 1.8 mmol/L in the group of diabetic patients taking statin therapy (24).

Target LDL cholesterol levels in our research were not reached in either the group of patients who have experienced a cardiovascular event or the group who have not experienced it, whereas target triglyceride levels were only reached in the group of patients who have not experienced a cardiovascular event.

Despite the use of statin and antihypertensive therapy in corresponding doses and adequate glucoregulation, diabetic patients are at additional cardiovascular risk due to increased triglyceride levels and decreased HDL cholesterol levels, which is why it is extremely important to regulate HDL cholesterol and plasma triglyceride levels in addition to LDL cholesterol levels, as well as to observe urate levels for possible worsening of the cardiovascular condition that would further contribute to micro- and macrocirculatory damage. Given the poor LDL cholesterol levels shown, it can be concluded that it is of great importance for patients with type 2 diabetes to regularly check their lipid profile and to increase statin doses, if necessary, in order to reach the target LDL cholesterol levels. In cases of triglyceridemia, fibrate therapy should be considered in addition to statin therapy. Nevertheless, the most important thing is to educate patients and administer non-pharmacological therapy for regulating body weight, as well as to encourage physical activity, which will, in the long term, have a positive effect on reducing triglyceride and urate levels, as well as on glucoregulation in patients with type 2 diabetes.

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