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Original research article

Changes in glucose-related parameters according to LDL-cholesterol concentration ranges in non-diabetic patients

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Abstract
The study focused on the changes in C-peptide, glycemia, insulin concentration, and insulin resistance according to LDL-cholesterol concentration ranges.

The metabolic profile of individuals in the Czech Republic (n = 1840) was classified by quartiles of LDL-cholesterol into four groups with the following ranges: 0.46–2.45 (n = 445), 2.46–3.00 (n = 474), 3.01–3.59 (n = 459), and 3.60–7.18 mmol/l (n = 462). The level of glucose, C-peptide, insulin, and area of parameters during OGTT and HOMA IR were compared with a relevant LDL-cholesterol range. The evaluation involved correlations between LDL-cholesterol and the above parameters, F-test and t-test.

Generally, mean values of glucose homeostasis-related parameters were higher with increasing LDL-cholesterol levels, except for mean HOMA IR values which rapidly increased (2.7–3.4) between LDL-cholesterol ranges of 3.00–3.59 and 3.60–7.18 mmol/l. Glucose, C-peptide, insulin concentrations, and the area of parameters reached greater changes especially after glucose load during OGTT ($p \leq 0.001$). Considerable changes were already observed for the above parameters between groups with LDL-cholesterol ranges of 2.46–3.00 and 3.01–3.59 mmol/l. HOMA IR increased with higher LDL-cholesterol concentrations, but the differences in mean values were not statistically significant. Most important differences appeared in glucose metabolism at LDL-cholesterol concentrations of 3.60–7.18 mmol/l in comparison to LDL-cholesterol lower ranges. In particular, the areas of C-peptide, glucose, and insulin ranges showed statistically significant differences between all groups with growing LDL-cholesterol ranges. The variances of HOMA IR statistically differed between groups created according to LDL-cholesterol concentrations ranges.

Keywords: C-peptide; Glucose; HOMA IR; Insulin; LDL-cholesterol

Highlights:
- Major alterations of glucose-related parameters were recorded, especially after glucose load (during OGTT).
- Significant changes in glucose metabolism appeared between the LDL-cholesterol concentrations ranges of 2.46–3.00 and 3.01–3.59 mmol/l.
- Areas of C-peptide, glucose, insulin showed statistically significant differences between all groups with increasing LDL-cholesterol ranges.
- Based on the results of the study, it's recommended to evaluate glycemic profile, especially in the cases of patients who are exposed repeatedly to higher LDL-cholesterol levels (lipotoxic effect).

Abbreviations:
HDL (High Density Lipoprotein); HOMA IR (Homeostasis Model Assessment of Insulin Resistance) Index; LDL (Low Density Lipoprotein); OGTT (Oral Glucose Tolerance Test); VLDL (Very Low-Density Lipoprotein)

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Introduction

The importance of metabolic studies has increased with a growing number of adults exposed to diabetes risks (463 million). According to the International Diabetes Federation, this group will rise to 700 million by 2045 (IDF Diabetes Atlas, 2024). However, impaired glucose regulation in patients with metabolic syndrome seems more complex, and the associations with other metabolites are yet to be completely clarified. Therefore, the objects of medical trials, especially in the last two decades, have not only focused on glucose metabolism but possible relationships with other substances (e.g., lipids, lipoproteins, hemoglobin) (Martha et al., 2022). Previously, the influence of cholesterol, triglycerides, or free fatty acids on insulin secretion has been described in a study by Parhofer (2015); and not just in patients with a disposition to diabetes but in NGT (normal glucose tolerance) individuals as well. Krawcyk et al. (2018) also evaluated plasma lipid profile and OGTT results to assess lipoproteins, triglycerides, and insulin resistance to predict metabolic syndrome. This retrospective study involved both obese and healthy lean peers. Similarly, Branchi et al. (2012) investigated the changes in serum lipoproteins and glucose profiles to verify different nutrient compositions in patients with and without metabolic syndrome.

In the conclusions of Perego et al. (2019), it is possible to find the differences in the group of lipoproteins qualified by density, when LDL seems to be directly relevant in beta-cell dysfunction due to cholesterol accumulation. Kruit et al. (2010) described significant abnormalities in both LDL and HDL particles in patients with diabetes. The conclusion suggested that the changes in lipoprotein particles could contribute to the pathogenesis of insulin resistance. To investigate the direct influence of LDL, Ye et al. (2018) eliminated LDL receptor-related protein (LRP1) and analyzed the interplay between beta-cell compensation and lipid metabolism. The results confirmed the effect of intracellular lipid metabolism on beta-cell functionality and viability in obesity and diabetes. Some authors have also mentioned the direct lipotoxic effect. Kim et al. (2003; 2005) have already confirmed the relationship between lipid substances and pancreas functions. A high concentration of lipids surrounding beta-cells was associated with increasing cell apoptosis. The acceleration of cellular breakdown was probably linked to higher concentrations of nitric oxide. The lipotoxic effect was also found in a study by Sharma and Alonso (2014), which strengthened the hypothesis that lipids may also impair compensatory beta-cell proliferation. Clinical observations of insulin secretory function support the role of lipids and free fatty acids in the risk and progression of both types of diabetes. Kupsal et al. (2015) summarized the conclusions of lipid and glycemia trials and confirmed that increased LDL concentration was also a characteristic feature of impaired insulin secretion. Chronic hyperlipidemia was considered toxic to beta cells and progressively accelerated the process of apoptosis. Therefore, many authors recommend considering glycemia and lipid metabolism together, especially in cases indicating possible insulin resistance (Díaz-Ruiz et al., 2019; Ikeoka and Krusinova, 2009).

Materials and methods

Patients, samples distribution, and laboratory analysis

Metabolic profiles of the correlative study were collected in the Czech Republic from 2009 until 2022, and all participants gave their consent to anonymous data analysis. The evaluation involves the experience of a local metabolic institute, and the test subjects primarily consisted of random members of the general population. The patients included were aged 17–75 (n = 1840) to ensure a representative profile of the population. Individuals receiving therapy or supplements to affect lipid or glucose metabolism were excluded.

Serum and plasma biochemical parameters were determined from venous blood. After information from surveys of the subjects was gathered, all samples were properly processed (centrifuging, serum preparation, etc.) and analyzed. The samples for the oral glucose tolerance test (OGTT) were taken in a fasting state (minimally 8 hours overnight) according to a valid OGTT methodology (sampling in a fasting state, 60 and 120 minutes after taking a sample). C-peptide and insulin concentrations were analyzed from plasma using the standard regulatory impact assessment methodology. The sensitivity of the provided tests for insulin was 1–10 μIU/ml and for C-peptide it was 0.1–0.5 ng/ml. The specificity of the RIA test for insulin and C-peptide is usually 95–98% and for C-peptide 95%. Glucose concentrations were analyzed enzymatically, as well as cholesterol levels (enzymatic assay). Homogenous methods were used for the detection of HDL and LDL-cholesterol in auto-analyzers. All serum biochemical parameters for the tests were provided according to the manufacturers' instructions, with strict adherence to time and quality limits (Roche Diagnostics, Abbott Laboratories).

Parameters for evaluation

To get a basic overview about glycemia and lipoprotein metabolism, all parameters in a fasting state were compared with their reference ranges. Naturally, the reference ranges of C-peptide (260–1730 pmol/l), glucose (3.9–5.6 mmol/l), insulin (2.5–24.0 mIU/l), and LDL-cholesterol (1.2–3.0 mmol/l) followed the standards valid in the Czech Republic (Methodology of glucose, total, HDL and LDL-cholesterol, 2020). Insulin resistance was assessed by the HOMA IR score (Homeostasis Model Assessment for Insulin Resistance) based on insulin and glucose concentrations. HOMA IR cut-off was set at 3.63, considered a signal of glucose metabolism alterations within the Czech population (Horáková et al., 2019). To consider alterations under physiological conditions, patients with glucose levels suggestive of hypoglycemia or diabetes (below 3.9 mmol/l or above 7.2 mmol/l) were removed from the study.

The methodology is based on a possible mechanism that lower, middle, and higher LDL-cholesterol level could affect beta-cell functions and, concordantly, glycemia parameters. The OGTT reflects a dynamic statement associated with glucose load, and possible alterations of glycemia could be affected by relevant LDL-cholesterol ranges. All parameters (glucose, insulin, C-peptide, HOMA IR) were divided by LDL-cholesterol quartiles to get the groups within the LDL-cholesterol concentration scale. The comparison included the changes in glucose-related parameters, which were relevant to the neighboring LDL-cholesterol concentration scales.

Díaz-Ruiz et al. (2019) used a similar trial structure to describe hydro-carbonated alterations at different cholesterol fractions. Zheng et al. (2017) also tested a hypothesis that dyslipidemia could affect beta-cell function, especially in non-diabetic subjects. A possible association between glycemia parameters and the variances of lipoproteins was also evaluated by Martha et al. (2022) using OGTT and HOMA IR levels.

Statistical analysis

At first, basic statistical parameters were calculated for all groups: number of values (n), arithmetic mean ($\bar{x}$), and

standard deviation (S_x). The quartiles identified LDL-cholesterol concentration groups and data distribution. To test the possible association between variables, Pearson's correlation coefficients (r_{xy}) were determined with limits of significance r_{xy} = 0.1 – low; r_{xy} = 0.3 – middle; and r_{xy} = 0.5 – high. The *F*-test (with quantile $F^{0.975}$) was performed to test the variance quality and select the correct type of *t*-test. The criteria for statistical significance (H_0 vs H_a) were set up as follows: $0.05 > p \geq 0.01$ (significant*), $0.01 > p > 0.001$ (moderately significant**), and highly significant*** ($p \leq 0.001$). The primary data was calculated using Microsoft Excel (MS Office, version 16). Software Statistica (version 14.00.15) provided information about the data distribution (quartiles, histogram), possible relationships, or the differences (the correlations, *F*-test, *t*-test), and enabled the graphical process of values.

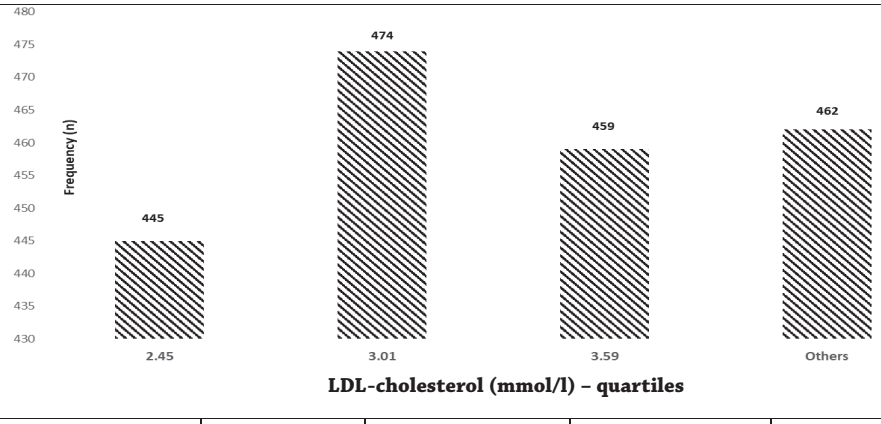
To maintain the quantity and data distribution, the file was not divided by gender, and critical values of characteristics were set for both genders and not separately.

Results

Data distribution LDL-cholesterol (mmol/l) of the tested file divided by quartiles is shown in Fig. 1. The share of individual samples divided into quartiles was balanced (*n* = 445, 474, 459, 462). Approximately half of the samples (*n* = 921) of LDL-cholesterol reached concentrations above the upper limit of the reference range (3.0 mmol/l). 459 samples fell within the LDL-cholesterol concentration range of 3.01–3.59 mmol/l, while 462 samples of LDL-cholesterol appeared between 3.60 and 7.18 mmol/l.

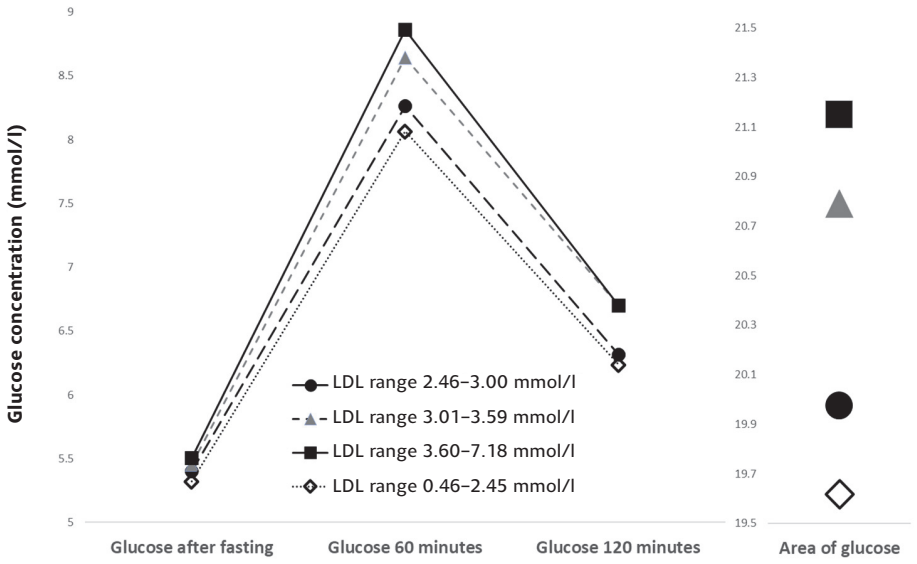
Group characteristics

The variables during OGTT and insulin resistance (HOMA IR) in the groups with various ranges of LDL-cholesterol are shown in Figs 2–5 and Suppl. Table S1.



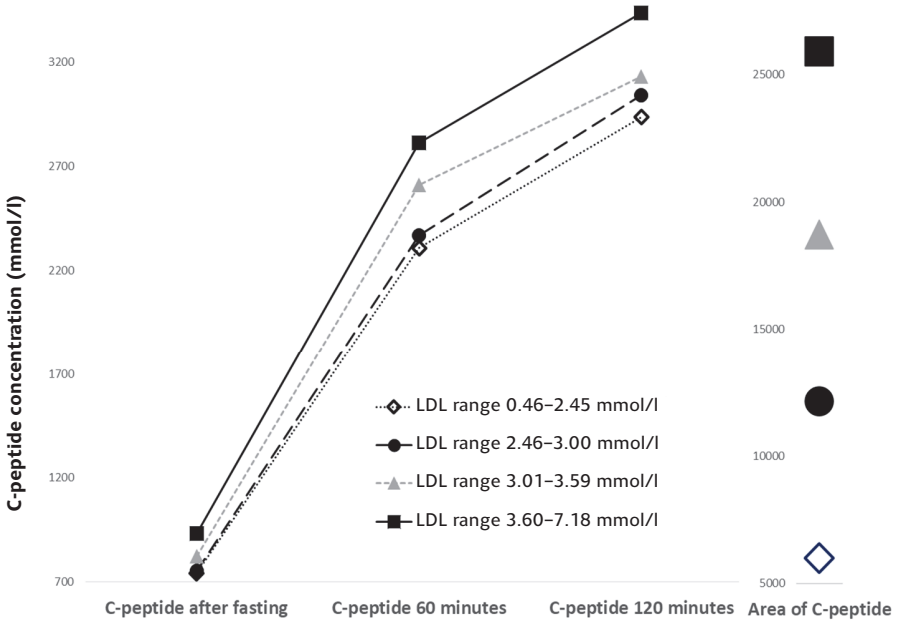
Minimum	Quartile 1	Quartile 2	Quartile 3	Maximum
0.46	2.45	3.01	3.59	7.18

Fig. 1. Data distribution LDL-cholesterol (mmol/l) of the tested file divided by quartiles



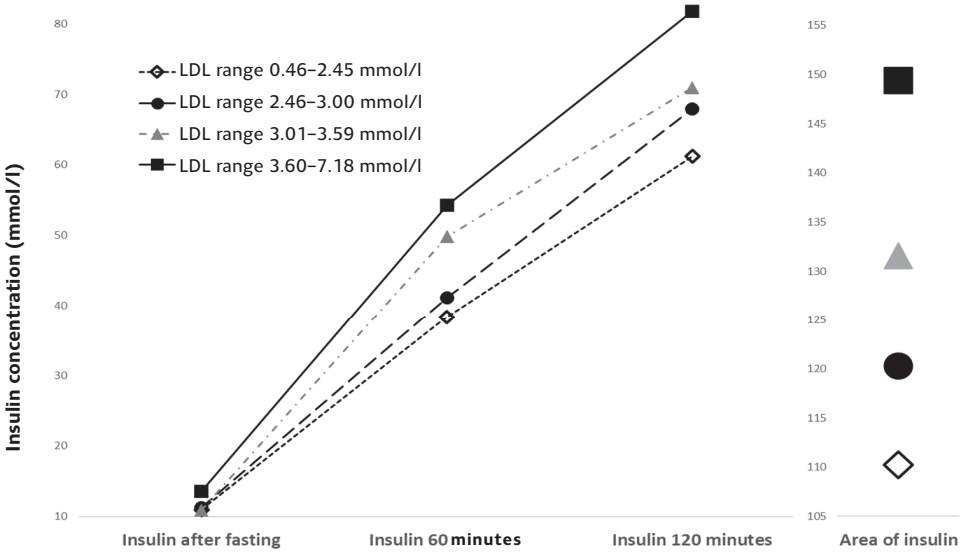
Legend: The change in glucose concentrations according to LDL ranges. As LDL levels decreased, glucose values during the OGTT also dropped. The area of parameters showed the same tendencies as the individual OGTT values in the glucose area, with the highest values found in the group with the highest LDL levels.

Fig. 2. Alterations in glucose concentrations for various ranges of LDL-cholesterol



Legend: The change in C-peptide concentrations according to LDL ranges. Significant changes in C-peptide occur 60 minutes after the OGTT, when C-peptide concentrations begin to vary according to LDL levels. The highest overall concentrations were recorded in the group with LDL levels between 3.60 and 7.18 mmol/l.

Fig. 3. Alterations in C-peptide concentrations for various ranges of LDL-cholesterol



Legend: The change in insulin concentrations according to LDL ranges. Significant changes in C-peptide occur especially 120 minutes after the OGTT, when insulin concentrations begin to vary according to LDL levels compared to a fasting state. The highest overall concentrations were recorded in the group with LDL levels between 3.60 and 7.18 mmol/l.

Fig. 4. Alterations in insulin concentrations for various ranges of LDL-cholesterol

Regardless of the LDL-cholesterol concentration levels, the age range was 17–75 years in all quartile groups (Suppl. Table S2). Insulin, glucose, C-peptide in a fasting state and insulin resistance (HOMA IR) were within the defined reference ranges. The mean glucose concentrations after fasting (5.3, 5.4, 5.5, and 5.5 mmol/l) fluctuated below the upper limit of the physiological range (5.6 mmol/l). The highest glucose level (5.5 mmol/l) was recorded in the group with LDL-cholesterol range of 3.60–7.18 mmol/l. Generally, the differences in glucose after fasting (up to 0.2 mmol/l) between the groups divided according to LDL-cholesterol concentrations were lower. More significant changes are possible to see in glucose concentration after 60 minutes (8.6 and 8.9 mmol/l) and 120 minutes (6.7 and 6.8 mmol/l) of OGTT in the groups with LDL-cho-

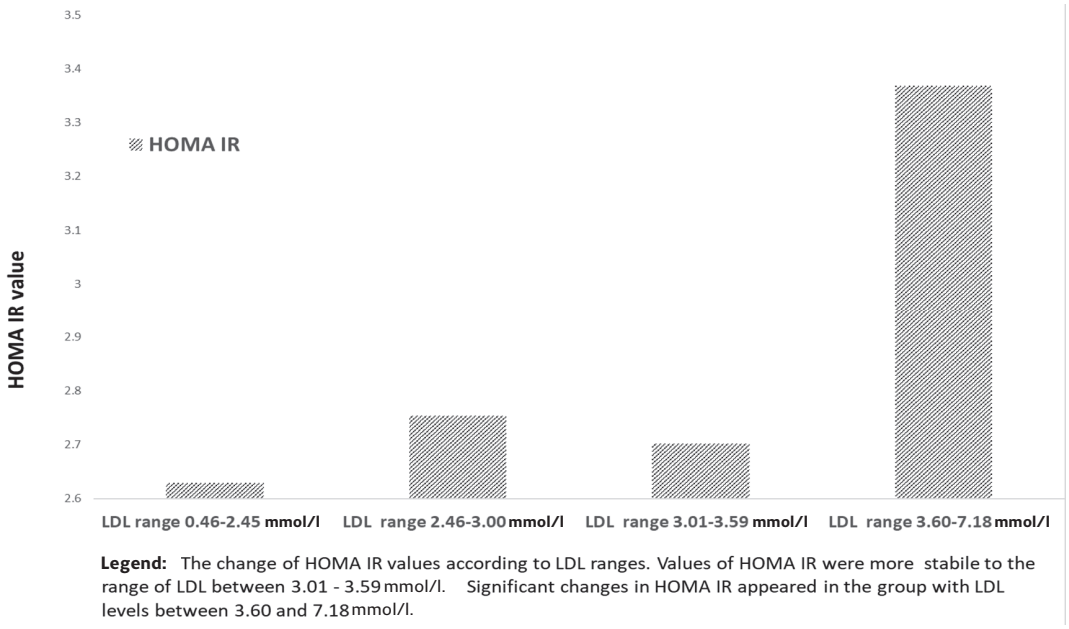


Fig. 5. HOMA IR values for various ranges of LDL-cholesterol

lesterol concentration range above 3.01 mmol/l in comparison to reference ranges of LDL-cholesterol (8.1, 8.3 mmol/l after 60 minutes and 6.2, 6.3 mmol/l after 120 minutes). The highest mean insulin concentration after fasting (13.5 mIU/l) was observed in the group with LDL-cholesterol range of 3.60 to 7.18 mmol/l. Lower insulin concentrations (about 19.3%) with slight changes were observed in the groups with LDL-cholesterol levels between 0.46–3.59 mmol/l (10.9, 11.2, 10.9 mIU/l). Insulin concentrations during OGTT (60 and 120 minutes) and area of insulin have a similar tendency to that of insulin after a fasting state when greater concentrations and relative increasing (about 12%) were recorded in the group with LDL-cholesterol above 3.6 mmol/l. The HOMA IR values didn't increase gradually with higher LDL-cholesterol ranges. Mean HOMA IR values didn't exceed the HOMA IR 3.63, considered a cut-off for the Czech Republic. However, 277 samples reached HOMA IR values of above 3.63. The changes in HOMA IR showed a trend similar to that of insulin (balanced to LDL-cholesterol range up to 3.59 mmol/l), and the highest value of insulin resistance (3.4) was observed in the group with LDL-cholesterol above 3.60 mmol/l. The highest variability of HOMA IR values was recorded at LDL-cholesterol levels between 3.6 and 7.18 mmol/l, where it exceeds the average value by more than twice (8.5). The mean C-peptide values in a fasting state showed a steady increase (743.3, 754.9, 823.5, 933.3 pmol/l) with higher LDL-cholesterol concentration ranges (from 0.46 to 7.18 mmol/l).

Generally, considerable differences in OGTT values and HOMA IR were recorded in LDL-cholesterol concentration ranges between 3.01–3.59 and 3.6–7.18 mmol/l. The values of glucose (60th and 120th minute of OGTT, area) and insulin (60th and 120th minute of OGTT, area) showed a tendency to increase with higher ranges of LDL-cholesterol. In the case of C-peptide, this trend was already found in a fasting state. However, some changes in glucose homeostasis-related parameters (HOMA IR, glucose, or insulin after fasting) were increased when the LDL-cholesterol concentration range reached above 3.60 mmol/l.

To test any possible correlations between C-peptide, insulin, glycemia, HOMA IR and LDL-cholesterol values, Pearson's correlation coefficients (r_{xy}) were determined (Table 1).

Table 1. Correlations between LDL-cholesterol and OGTT parameters

Pearson's correlation coefficients (r_{xy}) ($p < 0.05$) for LDL-cholesterol and OGTT parameters				
Glucose (mmol/l)	Fasting	60´	120´	Area of parameter
	0.10	0.14	0.11	0.14
C-peptide (pmol/l)	Fasting	60´	120´	Area of parameter
	0.12	0.17	0.15	0.17
Insulin (mIU/l)	Fasting	60´	120´	Area of parameter
	0.03	0.13	0.13	0.13
HOMA IR	0.03			

Note: (´) minutes of OGTT

All correlations involving LDL-cholesterol and metabolic parameters during OGTT (insulin, glucose, C-peptide, area of parameters) and HOMA IR seemed insignificant (up to r_{xy} = 0.3). A higher correlation coefficient was only found between LDL-cholesterol and C-peptide (r_{xy} = 0.17 – 60 minutes of OGTT and area of C-peptide). Subsequent regression analysis was not performed due to lower rxy (up to 0.5) results.

The *F*-test was used to test the equality of variances between groups with different LDL-cholesterol ranges (Table 2).

Table 2. *F*-test: Glucose-related parameters concentrations for various ranges of LDL-cholesterol

Glucose-related parameter	LDL-cholesterol concentration range (mmol/l)			
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – after fasting	2.46–3.00	0.77	–	0.63
	3.01–3.59	0.62	0.80	0.79
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – 60 minutes	2.46–3.00	**1.20***	–	0.76
	3.01–3.59	0.84	0.69	1.10
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – 120 minutes	2.46–3.00	1.14	–	0.81
	3.01–3.59	1.05	**0.92***	**0.89***
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – area	2.46–3.00	0.26	–	0.08
	3.01–3.59	0.08	0.30	0.29
		0.46–2.45	2.46–3.00	3.6–7.18
Glucose (mmol/l) – after fasting	2.46–3.00	**0.96***	–	0.46
	3.01–3.59	**0.96***	**0.99***	0.47
		0.46–2.45	2.46–3.00	3.6–7.18
Glucose (mmol/l) – 60 minutes	2.46–3.00	0.65	–	1.07/1.17
	3.01–3.59	0.75	**1.17***	0.91*
		0.46–2.45	2.46–3.00	3.6–7.18
Glucose (mmol/l) – 120 minutes	2.46–3.00	**1.21***	–	0.56
	3.01–3.59	**0.91***	0.75	0.74
		0.46–2.45	2.46–3.00	3.6–7.18
Glucose (mmol/l) – area	2.46–3.00	0.16	–	0.08
	3.01–3.59	0.06	0.28	0.28
		0.46–2.45	2.46–3.00	3.6–7.18
Insulin (mIU/l) – after fasting	2.46–3.00	**0.88***	–	0.85
	3.01–3.59	**1.39***	1.59*	0.54
		0.46–2.45	2.46–3.00	3.6–7.18
Insulin (mIU/l) – 60 minutes	2.46–3.00	**0.98***	–	1.07
	3.01–3.59	0.49	0.49/0.86	**0.91***
		0.46–2.45	2.46–3.00	3.6–7.18
Insulin (mIU/l) – 120 minutes	2.46–3.00	**0.91***	–	0.70
	3.01–3.59	0.72	0.80	0.86
		0.46–2.45	2.46–3.00	3.6–7.18
Insulin (mIU/l) – area	2.46–3.00	0.30	–	0.09
	3.01–3.59	0.10	0.30/0.86	0.29
		0.46–2.45	2.46–3.00	3.6–7.18
HOMA IR	2.46–3.00	**0.92***	–	0.7/0.86
	3.01–3.59	1.09	1.19*	**1.69***

Note: * 0.05 > *p*

A higher frequency of statistically significant changes ($p < 0.05$) of C-peptide variances was recorded after 60 minutes of OGTT between LDL-cholesterol ranges of 0.46–2.45 and 2.46–3.00 mmol/l. Similarly, the variances of C-peptide after 120 minutes of OGTT in the highest group of LDL-cholesterol (3.60–7.18 mmol/l) differed in comparison to the lower group (3.01–3.59 mmol/l). The same tendency was found between the concentration ranges of C-peptide 3.01–3.59 mmol/l and 2.46–3.00 mmol/l. The significant variances of glucose were already recorded in the state after fasting between the groups of LDL-cholesterol (0.46–2.45 and 2.46–3.00 mmol/l). The changes of variances also appeared at the higher range of LDL-cholesterol (2.46–3.00 and 3.01–3.59 mmol/l) in the state after fasting and after 120 minutes of OGTT. Statistically significant variances of glucose after 60 minutes were found between the groups of 2.46–3.00 and 3.01–3.59 mmol/l and the highest ranges of LDL-cholesterol (3.01–3.59 and 3.60–7.18 mmol/l). Similarly, the variances of insulin after fasting differed for glucose between the groups with different ranges of LDL-cholesterol (0.46–2.45 and 2.46–3.00 mmol/l, 2.46–3.00 and 3.01–3.59 mmol/l). The variances of insulin after fasting also varied between neighboring groups of LDL-cholesterol (2.46–3.00 and 3.01–3.59 mmol/l). Application of glucose during OGTT resulted in the difference of variances of LDL-cholesterol between the groups 0.46–2.45 and 2.46–3.00 mmol/l and between 3.01–3.59 mmol/l and the highest range of LDL-cholesterol (3.60–7.18 mmol/l). After 120 minutes of OGTT, statistically significant differences occurred only between the lowest (0.46–2.45 mmol/l) and the neighboring range (2.46–3.00 mmol/l) of LDL-cholesterol. The HOMA IR variances reached statistically significant differences between all neighboring groups created according to LDL-cholesterol concentration ranges.

From the observed variances of the glucose-related parameters, it follows that higher levels of LDL are accompanied by greater fluctuation of these values with regard to the type of parameter and the time of OGTT.

Based on the *F*-test results, the correct type of *t*-test was determined to compare the values within groups with various LDL-cholesterol concentration ranges (Tables 3, 4).

Table 3. *T*-test: C-peptide and glucose concentrations for various ranges of LDL-cholesterol

Glucose-related parameter	LDL-cholesterol concentration range (mmol/l)			
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – after fasting	2.46–3.00	–0.34	–	**–4.43*** **
	3.01–3.59	**–2.17***	–1.82	**–2.59****
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – 60 minutes	2.46–3.00	–0.85	–	**–6.20*** **
	3.01–3.59	**–3.90*** **	**–3.30****	**–2.60****
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – 120 minutes	2.46–3.00	–1.35	–	**–5.07*** **
	3.01–3.59	**–2.44***	–1.17	**–3.84*** **
		0.46–2.45	2.46–3.00	3.6–7.18
C-peptide (pmol/l) – area	2.46–3.00	**–28.15*** **	–	**–54.59*** **
	3.01–3.59	**–50.10*** **	**–31.28*** **	**–33.31*** **
		0.46–2.45	2.46–3.00	3.60–7.18
Glucose (mmol/l) – after fasting	2.46–3.00	**–2.05***	–	**–2.16***
	3.01–3.59	**–3.31****	–1.28	–1.13
		0.46–2.45	2.46–3.00	3.60–7.18
Glucose (mmol/l) – 60 minutes	2.46–3.00	**–3.19****	–	**–6.93*** **
	3.01–3.59	**–8.26*** **	**–4.53*** **	**–2.57***
		0.46–2.45	2.46–3.00	3.60–7.18
Glucose (mmol/l) – 120 minutes	2.46–3.00	–0.73	–	**–3.83*** **
	3.01–3.59	**–3.91*** **	**–3.43*** **	–0.65
		0.46–2.45	2.46–3.00	3.60–7.18
Glucose (mmol/l) – area	2.46–3.00	**–35.77*** **	–	**–65.87*** **
	3.01–3.59	**–61.60*** **	**–38.15*** **	**–40.32*** **

Note: * $0.05 > p \geq 0.01$; ** $0.01 > p > 0.001$; *** $p \leq 0.001$

Table 4. *T*-test: Insulin concentrations and HOMA IR for various ranges of LDL-cholesterol

Glucose-related parameter	LDL-cholesterol concentration range (mmol/l)			
		0.46–2.45	2.46–3.00	3.60–7.18
Insulin (mIU/l) – after fasting	2.46–3.00	–0.14		–1.07
	3.01–3.59	0.04	–0.19	–1.35
		0.46–2.45	2.46–3.00	3.60–7.18
Insulin (mIU/l) – 60 minutes	2.46–3.00	–1.19	–	**–4.71*****
	3.01–3.59	**–3.95*****	**–3.03****	–1.35
		0.46–2.45	2.46–3.00	3.60–7.18
Insulin (mIU/l) – 120 minutes	2.46–3.00	**–2.16***	–	**–3.96*****
	3.01–3.59	**–2.91****	–0.89	**–2.94****
		0.46–2.45	2.46–3.00	3.60–7.18
Insulin (mIU/l) – area	2.46–3.00	**–15.77*****	–	**–31.56*****
	3.01–3.59	**–28.77*****	**–18.00*****	**–19.23*****
		0.46–2.45	2.46–3.00	3.6–7.18
HOMA IR	2.46–3.00	0.03	–	–1.47
	3.01–3.59	–0.17	–0.20	–1.34

Note: * $0.05 > p \geq 0.01$; ** $0.01 > p > 0.001$; *** $p \leq 0.001$

The mean values of C-peptide showed statistically significant changes ($p \leq 0.001$), especially between groups with LDL-cholesterol concentrations above 2.46–3.00 mmol/l. Significantly, the area of C-peptide seemed to be a parameter that reached statistically significant changes in all concentration groups of LDL-cholesterol. The mean glucose concentrations differed, especially after 60 and 120 minutes of OGTT between the groups of LDL-cholesterol (0.46–2.45 and 3.01–3.59 mmol/l). Just as with C-peptide, the glucose area was evaluated as a parameter with statistically significant changes in all groups divided according to the LDL-cholesterol ranges. It was possible to observe the highest frequency of changes in insulin concentrations after 60 and 120 minutes of OGTT between LDL-cholesterol concentration ranges of 2.46–3.00 mmol/l and 3.60–7.18 mmol/l. Similar statistical results with high significance ($p \leq 0.001$) also appeared in the area of insulin between all groups of LDL-cholesterol. Only HOMA IR results didn't record statistically significant changes between the groups created according to different LDL-cholesterol concentrations.

Discussion

Although age is one of the factors influencing possible changes in carbohydrate metabolism, no significant differences were recorded in the mean age range of patients divided by LDL-cholesterol levels (17–75 years). A possible reason is the exclusion of individuals from the study who have a possible tendency to diabetes or hypoglycemia (glucose levels below 3.9 and above 7.2 mmol/l).

Glucose levels in the tested samples (5.3, 5.4, 5.5, and 5.5 mmol/l), regardless of LDL-cholesterol concentration ranges, corresponded with the results (5.2–5.9 mmol/l) in non-diabetic patients of a cohort study in the Czech Republic for the years 2018 and 2022. The insulin levels (10.9, 11.2, 10.9, 13.5 mIU/l) differed slightly compared to the concentrations in the same survey (7.9–11.7 mIU/l). However, the mean levels of insulin in all groups appeared in the reference range (2.5–24.0 mIU/l) valid for the Czech Republic (Horáková et al., 2019; 2022).

Kupsal et al. (2015) also recorded the changes in glucose homeostasis-related parameters at higher long-lasting LDL-cholesterol and plasma glyceride concentrations. This review describes the adverse effect of hyperglycemia and hyperlipidemia (or both) on beta-cell function. Abbasi et al. (2019) also reached a similar conclusion regarding glycemia changes during OGTT in healthy individuals. Plasma insulin, glucose, and triglyceride concentrations were significantly linked to higher LDL-cholesterol and lower HDL-cholesterol levels. Parhofer et al. (2015) also aimed to describe lipid and glucose metabolism and confirmed that elevated triglycerides, low HDL-cholesterol, and predominance of LDL-cholesterol particles characterized the clinical manifestation of impaired glycemia; however, with an opinion that this relationship seems to be more complex, and it is necessary to involve more variables to consider this influence. Perego et al. (2019) also noted that LDL-cholesterol receptors and LDL-cholesterol concentrations appeared to play a relevant role in beta-cell function and, concordantly, in glycemia regulation. Wildberg et al. (2019) also investigated lipoprotein levels during OGTT and the possible development of diabetes in the pre-symptomatic state. In summary, lipoprotein levels were significantly associated with 120th-minute glucose and 120th-minute insulin concentrations. Sapkota and Thapa (2017) also confirmed a growing tendency between glucose-related parameters and lipid profile when fasting, and postprandial blood sugar changed according to VLDL and LDL-cholesterol concentrations.

However, the levels of lipoproteins and glycide profiles have not always shown a clear correlation and have often depended on other parameters. Wang et al. (2020) assessed lipids and fasting plasma glucose levels and found a partial relationship between glycemia and lipid profile. In this study, fasting plasma glucose was significantly associated with HDL

and total cholesterol, but not with LDL-cholesterol and total glycerides. Dannecker et al. (2021) investigated glucagon concentrations, insulin secretion, and insulin clearance indices derived from the OGTT in patients without cholesterol-lowering therapy but with an increased risk of diabetes. There was no relationship between LDL-cholesterol and fasting glucagon or post–glucose load glucagon levels. However, this study detected significant positive associations between LDL-cholesterol and C-peptide–based indices of insulin secretion. Martha et al. (2022) evaluated HOMA IR results and concluded that HOMA IR values during OGTT were positively correlated with LDL-cholesterol, total glycerides, and cholesterol concentrations. Any statistically significant changes between the mean values of HOMA IR according to LDL-cholesterol ranges were found in this study.

Based on the changes in the selected parameters, evaluating both the mean values and variances of glucose-related parameters in relation to LDL concentration ranges is recommended. The range of LDL value dispersions indicates that high levels of LDL also have a physiological impact concerning the fluctuation or range of indicators associated with glycemia.

Except for the correlations between lipoprotein and glucose metabolism results, it is desirable to know which concentration of LDL-cholesterol is a probable cut-off of glycemia alterations or insulin resistance. This level can be a valuable tool for possible analysis of glucose metabolism, especially when some patients are exposed to high lipoproteins levels for time-extended periods.

Conclusion

Considerable changes in glucose homeostasis-related parameters were already observed between the groups with LDL-cholesterol ranges of 2.46–3.00 and 3.01–3.59 mmol/l. The most important differences appeared in glucose metabolism at LDL-cholesterol concentrations of 3.60–7.18 mmol/l compared to LDL-cholesterol lower ranges. C-peptide, glucose, and insulin ranges showed statistically significant differences between all groups with increasing LDL-cholesterol ranges. Generally, glycemia, C-peptide, and insulin concentrations differed within the LDL-cholesterol concentration ranges. Based on the mentioned results, LDL-cholesterol can be considered an important auxiliary parameter for glycide alterations. Evaluated parameters and the ranges of glycemia and lipoproteins (LDL-cholesterol) might be used as a part of preventive analysis or during therapy for metabolic syndrome.

Author's contributions

VK: conceived and designed the research; *MV, PS, RV, EF, DM, DH, LŠ, KV*: collected the data; *VK* analyzed the data; *VK* wrote the paper; *KK* and *LH* considered the quality and style of the article. All authors have read and agreed to the published version of the manuscript.

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Ethical aspects and conflict of interest

The authors have no conflict of interest to declare.

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