CLINICAL STUDY

Association of lipid parameters with insulin resistance in the Kazakh population

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ABSTRACT

BACKGROUND: Insulin resistance (IR) is a consequence of chronic adipose tissue inflammation and underlies the pathogenesis of several diseases, such as type 2 diabetes mellitus, cardiovascular diseases and metabolic syndrome. In this study, we examined the association between dyslipidaemia and IR; directly comparing conventional lipid ratios and apoB/apoA1 ratios for strength and independence as risk factors for IR in a Kazakh population.

METHODS: The design of this study was a case-control study. There were 507 participants in the study. We examined each participant's plasma total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, apolipoprotein B, and apolipoprotein A1. IR was determined using an IR homeostasis model assessment (HOMA-IR). To assess the risk of an atherogenic blood lipid profile, atherogenicity coefficients were calculated: Bad cholesterol to good cholesterol ratio ((TC-HDL)/HDL); TG to HDL ratio (TRG/HDL); apoB to apoA1 ratio (apoB/apoA1).

RESULTS: In this study, high waist circumference and BMI were more common in men. The group with IR had significantly higher waist circumference (cm) (p = 0.0001) and BMI (kg/m²) (p = 0.04) than the group without IR. The risk of IR was significantly associated with the apoB/apoA1 ratio (p = 0.03). Analysis of the association between HOMA-IR and apoB/apoA1 ratio increased the risk of IR at apoB/apoA1 ratios of 0.71 to 0.85 and above 0.86 by a factor of 1.93 and 1.84, respectively. HOMA-IR levels were weakly significantly correlated with TG levels (rS = 0.3; p = 0.0001) and very weakly positively correlated with apoB levels (rS = 0.1; p = 0.002) and apoB/apoA1 (rS = 0.1; p = 0.001), there was a weak negative correlation with apoA1 levels (rS = -0.1; p = 0.02). Logistic regression analysis showed that the risk of developing IR was significantly lower in men than in women, adjusted OR (95% CI) = 0.75 (0.49–1.0) p = 0.02. CONCLUSION: In our study, IR was more common in Kazakh women than in Kazakh men. IR was also associated with apoB and TG levels. Thus, we suggest that analysis of TG, apoB and apoB/apoA1 ratio may be recommended as early predictors of IR risk in the Kazakh population (*Tab. 3, Ref. 22*). Text in PDF *www. elis.sk*

KEY WORDS: insulin resistance, dyslipidaemia, apolipoproteins, triglycerides, lipids.

Introduction

Cardiovascular disease (CVD) is known to occur more frequently in overweight, obese, insulin-resistant (IR) individuals, irrespective of their age (1). The prevalence of obesity and diabetes mellitus (DM) as risk factors for CVDs is increasing worldwide. Prevention is therefore important in eliminating or minimizing risk factors for CVDs and related events (2). IR and its associated consequences are more common in developed countries, with a global prevalence between 30 % and 40 % (3). IR, dyslipidaemia, abdominal obesity and arterial hypertension (AH) are risk factors, the combination of which is called metabolic syndrome (MS). The presence of MS increases the risk of both CVD and fatal complications in patients with existing circulatory disease. The interrelationships of these risk factors are being studied, and the contribution of the genetic component in the pathogenesis of these diseases is important. Lorenzo C. et al. conducted studies where they applied the MS criteria of four programmes: The National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATPIII), International Diabetes Federation (IDF) and WHO (4). They argue that although these programmers have different sensitivity in detecting MS, they can predict CVDs and diabetes. They argue that although these programs have different sensitivity in detecting MS, they can predict CVDs and DM.

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Acknowledgements: This work was supported as part of an intra-university startup project of NCJSC "Medical University of Semey" by the Ministry of Healthcare of the Republic of Kazakhstan (ID0118PKИ0541) «Development of markers for predicting the risk of metabolic syndrome development in the Kazakh population».

Globally, there is an increasing trend in obesity and type 2 DM associated with lifestyle, sedentary behavior and the consumption of high-calorie foods (5). Reduced insulin sensitivity primarily affects the liver, muscle and adipose tissue. IR develops years before the onset of type 2 DM and is associated with obesity, abdominal obesity, but can also occur in lean people with AH. In overweight patients, adipocytes begin to hypertrophy with a constant intake of excessive caloric foods. The hypertrophied adipocytes accumulate large stores of triglycerides (TG), have a high lipolytic function, and plasma concentrations of low-density lipoprotein (LDL), TGs, and their residues, very low-density lipoprotein (VLDL), apolipoprotein B (apoB) increase and high-density lipoprotein (HDL) levels decrease (5-7). And this all leads to visceral adipocyte cell death and cytokine expression. All pro-inflammatory and metabolic consequences of obesity and IR lead to endothelial abnormalities, which are key triggers of atherosclerosis (5-7). This upsets the balance between vasoconstrictors and vasodilators, growthpromoting and growth-inhibiting factors, pro-atherogenic and anti-atherogenic factors (5).

Atherogenic dyslipidaemia, which includes levels of LDL, VLDL, intermediate lipoprotein fraction, is often not increased in MS compared with apoB levels, which in turn may lead to underestimation of the risk of atherogenic CVDs (ACVDs) (6). Given the key role of apoB-containing lipoproteins in the development and progression of atherosclerosis, measuring apoB-containing lipoprotein concentrations is essential for assessing the risk of ACVDs and monitoring treatment (2). Apolipoprotein A1 (apoA1) is the protein part of HDL and just like HDL it is inversely related to the risk of ACVDs (8).

IR is a consequence of chronic inflammation of adipose tissue and underlies the pathogenesis of a range of diseases, including type 2 diabetes (9). Excess insulin, which is common in IR, suppresses gluconeogenesis in the liver, reduces glucose uptake in skeletal muscle and, by increasing free fatty acid levels, inhibits lipolysis (10). The combination of these disorders leads to dyslipidaemia, which in turn is a trigger mechanism in the development of CVDs and MS (11,12). Pang S.J. et al. studied the association of BP with lipid indices using TG/HDL, LDL/HDL in elderly patients and they concluded that the association of BP with lipid indices varies with glucose levels. They recommend paying attention to TG, HDL, LDL/HDL, LDL/HDL levels when glucose levels are normal, and, in patients with diabetes, to TG, HDL, HDL/HDL levels (13).

In this study, we investigated association between dyslipidemia and IR; directly compared the traditional lipid ratios and apoB/ apoA1 ratio for strength and independence as risk factors for IR in the Kazakh population.

Materials and methods

Study population.

A total of 507 subjects living in Semey city, Kazakhstan, during 2018–2020 and belonging to Kazakh ethnicity aged at onset from 18 to 65 years. The exclusion criteria included cancer, cardiovascular and renal failure, mental diseases, pregnancy, or lactation. All participants were informed of the purpose and methods of the study. Each participant signed a written informed consent to participate in this study. The present study complied with the principles outlined in the Helsinki Declaration of the World Medical Organization. This study was approved by the Ethics Committee of the Semey Medical University which approved the research protocol (Protocol # 11 from 27.09.2017).

Data collection.

Relevant demographic and clinical characteristics were included: systolic and diastolic blood pressure, height, weight, and waist circumference. Body mass index (BMI) was calculated by the formula: weight (kg)/ height (m)². Whole venous blood samples were taken from each of the participants in the morning of fasting. Arterial blood pressure was measured twice after 5 minutes of rest with subjects seated.

Laboratory.

Total cholesterol (TC), TG, HDL, LDL, apoB, apoA1, insulin and glucose were measured on Cobas 8000 analyzers (Roche Diagnostics GmbH, Germany) according to manufacturer's instructions. Reference values: glucose 3.89-5.83 mmol/l, insulin 2.6–24.9 IU/ml, TC 2.9–5.2 mmol/l, TG 1.7–2.25 mmol/l, HDL 0.78–2.2 mmol/l, and LDL 2.33–5.31 mmol/l, apoA1 1.04–2.02 g/l (for men) and 1.08–2.25 g/l (for women), apoB 0.66–1.33 g/l (for men) and 0.6–1.17 g/l (for women). Insulin sensitivity index was determined using the homeostasis model assessment IR (HOMA-IR) and was calculated as plasma glucose (mmol/l) x insulin (mU/l)/22.5. In our study, a dichotomous classification of IR was performed when HOMA-IR > 2.7, in addition to assessing HOMA-IR as a continuous variable.

Atherogenicity coefficients have been calculated to assess the risk of an atherogenic blood lipid profile (14–16): Ratio of bad cholesterol to good cholesterol ((TC-HDL)/HDL); TG to HDL ratio (TRG/HDL); apoB to apoA1 ratio (apoB/apoA1). (TC-HDL)/HDL was calculated as follows: in [TC (mmol/l) – HDL (mmol/l) / HDL (mmol/l)]. TRG/HDL was calculated using the following formula: in [triglycerides (mmol/l)) / HDL (mmol/l)]. ApoB/apoA1 was calculated as follows: in [apoB (g/l) / apoA1 (g/l)]. High risks of an atherogenic lipid profile are considered to be for (TC-HDL)/HDL > 3.0; for TRG/LDL > 3.0; for apoB/apoA1 > 0.85

Statistical analysis.

All statistical analyses were performed using IBM SPSS Statistics Version 20 (International Business Machines Corp., Armonk, NY, USA) and SNPStat (SNPStats: your web tool for SNP analysis). All variables were examined to determine whether they were normally distributed. Continuous non-normally distributed variables were represented as median (Q1–Q3). To compare the means of non-normally variables between two groups the Mann-Whitney test was performed. The χ^2 test was used for comparing differences in categorical variables between groups. Spearman correlation coefficients were calculated to assess the strength and direction of the linear relationship between continuous quantitative variables of biochemical indicators. The logistic regression 604-608

analysis was used to analyse the relationships between continuous variables. Statistical significance was defined as p<0.05 for a single test.

Results

Comparisons of the subjects, general information.

The study population included 245 males (age: Me $(Q_1, -Q_3) =$ 48 years (39–57)) and 262 females (age: Me $(Q_1, -Q_3) =$ 45 years (38–53)), p = 0.03. Table 1 shows demographic and laboratory find-

| Tab. 1. Demographic an | nd laboratory finding | s of the study 1 | population (n = 5 | 507). |
|------------------------|-----------------------|------------------|-------------------|-------|
| | | | | |

| Ger | | |
|---------------------|---|---|
| Males | Females | p* |
| Me (Q1–Q3) | Me (Q1–Q3) | |
| 48 (39–57) | 46 (38–53) | 0.03 |
| 100 (93-109.5) | 93 (88–98) | 0.0001 |
| 25.42 (24.01-29.32) | 25.87 (22.73-28.68) | 0.04 |
| 5.64 (4.49-6.34) | 5.41 (4.34-6.39) | 0.32 |
| 8.70 (5.65–13.9) | 9.70 (6.2–16.45) | 0.1 |
| 2.10 (1.34-3.49) | 2.26 (1.34-4.16) | 0.4 |
| 3.29 (2.47-4.68) | 3.41 (2.59–4.32) | 0.5 |
| 1.23 (0.83-1.76) | 1.23 (0.87-1.73) | 0.86 |
| 0.95 (0.69–1.49) | 0.9 (0.7–1.3) | 0.24 |
| 1.82 (1.41-2.49) | 1.86 (1.32-2.52) | 0.98 |
| 0.99 (0.78-1.17) | 0.96 (0.79-1.16) | 0.59 |
| 1.45 (1.27–1.67) | 1.53 (1.35–1.74) | 0.001 |
| 2.32 (1.22-3.87) | 2.55 (1.37-3.92) | 0.45 |
| 1.22 (0.76-2.04) | 0.79 (1.34-2.16) | 0.42 |
| 0.67 (0.53-0.84) | 0.62 (0.49-0.81) | 0.09 |
| | Males Me (Q1–Q3) 48 (39–57) 100 (93–109.5) 25.42 (24.01–29.32) 5.64 (4.49–6.34) 8.70 (5.65–13.9) 2.10 (1.34–3.49) 3.29 (2.47–4.68) 1.23 (0.83–1.76) 0.95 (0.69–1.49) 1.82 (1.41–2.49) 0.99 (0.78–1.17) 1.45 (1.27–1.67) 2.32 (1.22–3.87) 1.22 (0.76–2.04) 0.67 (0.53–0.84) | Me (Q1-Q3)Me (Q1-Q3)48 (39-57)46 (38-53)100 (93-109.5)93 (88-98)25.42 (24.01-29.32)25.87 (22.73-28.68)5.64 (4.49-6.34)5.41 (4.34-6.39)8.70 (5.65-13.9)9.70 (6.2-16.45)2.10 (1.34-3.49)2.26 (1.34-4.16)3.29 (2.47-4.68)3.41 (2.59-4.32)1.23 (0.83-1.76)1.23 (0.87-1.73)0.95 (0.69-1.49)0.9 (0.7-1.3)1.82 (1.41-2.49)1.86 (1.32-2.52)0.99 (0.78-1.17)0.96 (0.79-1.16)1.45 (1.27-1.67)1.53 (1.35-1.74)2.32 (1.22-3.87)2.55 (1.37-3.92)1.22 (0.76-2.04)0.79 (1.34-2.16) |

Median (Q1–Q3) for age, waist circumference, BMI, glucose, insulin, HOMA-IR, total cholesterol, triglycerides, HDL, LDL, apolipoprotein B, apolipoprotein A1, (TC-HDL)/HDL, TRG/HDL, apoB/apoA1. p less than 0.05 were considered statistically significant. * Mann-Whitney test

Tab. 2. Demographic and laboratory findings of the groups HOMA-IR (n = 507).

| | HOMA-IR | | * |
|----------------------------|---------------------|---------------------|--------|
| | ≤2.7 Me (Q1–Q3) | >2.7 Me (Q1–Q3) | p * |
| Age, years | 46 (38–55) | 47 (39–56) | 0.03 |
| Gender (n) | 311 | 196 | |
| Males | 161 | 84 | 0.05** |
| Females | 150 | 112 | |
| Waist circumference (cm) | 96 (90-107) | 95 (90–103) | 0.0001 |
| BMI (kg/m2) | 26.15 (23.61-28.93) | 26.12 (22.79-29.06) | 0.04 |
| Glucose (mmol/l) | 5.01 (4.01-5.99) | 6.0 (5,16-6.88) | 0.0001 |
| Insulin (IU/ml) | 8.7 (5.65-13.9) | 9.7 (6.2–16.45) | 0.0001 |
| Total cholesterol (mmol/l) | 3.52 (2.59-4.58) | 3.31 (2.46-4.43) | 0.15 |
| Triglycerides (mmol/l) | 1.1 (0.79–1.53) | 1.49 (0.95-2.02) | 0.0001 |
| HDL (mmol/l) | 0.9 (0.7–1.4) | 0.93 (0.7-1.41) | 0.89 |
| LDL (mmol/l) | 1.86 (1.42-2.6) | 1.86 (1.22–2.4) | 0.04 |
| Apolipoprotein B (g/l) | 0.94 (0.76-1.14) | 1.03 (0.84–1.2) | 0.004 |
| Apolipoprotein A1 (g/l) | 1.52 (1.33–1.74) | 1.47 (1.28–1.63) | 0.04 |
| (TC-HDL)/HDL | 2.58 (1.41-4.1) | 2.36 (1.22-3.73) | 0.18 |
| TRG/HDL | 1.12 (0.69–1.9) | 1.57 (0.94–2.37) | 0.0001 |
| apoB/apoA1 | 0.63 (0.49-0.8) | 0.7 (0.54–0.87) | 0.002 |

Median (Q1–Q3) for age, waist circumference, BMI, glucose, insulin, total cholesterol, triglycerides, HDL, LDL, apolipoprotein B, apolipoprotein A1, (TC-HDL)/HDL, TRG/HDL, apoB/apoA1. p less than 0.05 were considered statistically significant. * Mann-Whitney test. ** χ^2 test

ings of the study population between gender groups. In terms of age, waist circumference, and BMI there were significant statistical differences between the gender groups. High waist circumference and BMI were more common in males. There were no statistical differences between gender groups in levels of glucose, insulin, HOMA-IR, TC, TG, HDL, LDL, apoB, (TC - HDL)/HDL, TRG/HDL, apoB/apoA1 (Tab. 1). Only the level of apoA1 was significantly higher for females than males. The group with IR had significantly higher waist circumference (cm) (p = 0.0001) and BMI (p = 0.04) levels (kg/m2) than the group without IR (Tab. 2). The

mean levels of triglycerides (mmol/l), LDL (mmol/l), apoB (g/l), TRG/HDL and apoB/ apoA1 were significantly higher and lower for apoA1 (g/l) in the IR group (Tab. 2).

Association between biochemical levels in the groups of IR

As seen in Table 3, a significant relationship between HOMA-IR and apoB/apoA1 ratio was found. The risk of IR was significantly associated with an apoB/apoA1 ratio (p = 0.03). Analyzing the linkage between HOMA-IR and apoB/apoA1 ratio increased the risk of IR in apoB/apoA1 ratio of 0.71 to 0.85 and above 0.86, 1.93 times and 1.84 times, respectively. HOMA-IR levels were weakly significantly correlated with TG levels ($r_s = 0.3$; p = 0.0001) and very weakly positively correlated with apoB levels ($r_s =$ 0.1; p = 0.002) and apoB/apoA1 levels (r_s = 0.1; p = 0.001), and a weak negative correlation with apoA1 levels ($r_s = -0.1$; p = 0.02) was observed. No significant correlations were found with the other biochemical parameters.

Logistic regression between the levels of IR and biochemical markers of lipid profile.

In constructing logistic regression models, risk factors such as gender, age, BMI were included as independent variables and dependent variables as biochemical indicators. A total of 6 logistic regression models were built, of which 1 model was statistically significant. Based on the Nigelkerk determination coefficient values, the model takes into account 10 % of the factor determining the probability of IR development. Based on the regression coefficient values, the factor sex has a significant relationship with the probability of developing IR. Logistic regression analysis showed that the risk of IR was significantly lower in male gender than in female gender, adjusted OR (95% CI) = 0.75 (0.49–1.0) p = 0.02.

| | | HOMA-IR | | OR (95% CI) | |
|-------------------------|---|----------|----------|------------------|----------|
| | | ≤2.7 (n) | >2.7 (n) | | - p* |
| Total cholesterol | ≤4.9 | 269 | 177 | 1.00 | - 0.2 |
| (mmol/l) | >4.9 | 42 | 19 | 0.69 (0.39-1.22) | |
| Triglycerides (mmol/l) | ≤1.7 | 252 | 122 | 1.00 | 0.0001 |
| | >1.7 | 59 | 74 | 2.59 (1.73-3.88) | - 0.0001 |
| HDL (mmol/l) | $\begin{array}{l} Male \geq \!\! 1.0 \\ Female \geq \!\! 1.2 \end{array}$ | 115 | 70 | 1.00 | |
| | Male <1.0 Female <1.2 | 196 | 126 | 1.06 (0.73–1.53) | 0.77 |
| I.D.I. (mm.ol/l) | ≤3.0 | 263 | 177 | 1.00 | 0.07 |
| LDL (mmol/l) | >3.0 | 48 | 19 | 0.59 (0.33-1.03) | - 0.06 |
| Apolipoprotein B (g/l) | <0.9 | 137 | 61 | 1.00 | - 0.004 |
| | ≥0.9 | 174 | 135 | 1.74 (1.2–2.54) | |
| Apolipoprotein A1 (g/l) | $Male \ge 1.04 \\ Female \ge 1.08$ | 291 | 188 | 1.00 | - 0.26 |
| | Male <1.04 Female <1.08 | 20 | 8 | 0.62 (0.27–1.43) | - 0.20 |
| (TC - HDL)/HDL | ≤3.0 | | | | _ |
| | >3.0 | | | | - |
| TRG/HDL | ≤3.0 | 283 | 171 | 1.00 | - 0.18 |
| | >3.0 | 28 | 25 | 1.48 (0.83-2.62) | - 0.18 |
| apoB/apoA1 | ≤0.56 | 125 | 55 | 1.0 | |
| | 0.57≤0.70 | 76 | 50 | 1.49 (0.93-2.41) | - 0.02 |
| | 0.71 ≤ 0.85 | 47 | 40 | 1.93 (1.14-3.28) | - 0.03 |
| | ≥0.86 | 63 | 51 | 1.84 (1.31-2.99) | - |
| | | | | × / | |

Tab. 3. The frequency laboratory findings in the groups HOMA-IR (n = 507).

* χ² test OR (95% CI) - Odds ratio (95% confidence interval)

Discussion

When examining the relationship between HOMA-IR groups and risk factors, a significant association with gender was found. According to our results, HOMA-IR was more strongly associated with the female gender compared to the male gender. In our study, Kazakh men had a 30 % lower risk of developing IR compared to Kazakh women. Researches in recent years had shown that healthy members of the Kazakh population are more likely to have high glucose levels, low TG, high HDL, high BMI, high waist size (17, 18).

In this study, mean levels of TG, LDL, apoB, apoA1, apoB/ apoA1, TRG/HDL, glucose and insulin differed in the HOMA-IR groups. IR was more often accompanied by hypertriglyceridemia, low LDL and apoA1 levels, hyperpolipoproteinemia B, high apoB/ apoA1 and TRG/HDL levels, hyperglycaemia, and hyperinsulinaemia. Our results are consistent with those of other researchers. In a study examining the relationship between IR and carbohydrate, lipid metabolism, the authors found that abdominal obesity, hyperglycaemia, high LDL levels, hypertriglyceridaemia, hypercholesterolaemia, low HDL levels were more frequently observed in the Kazakh population (18). Similar results were obtained by Yan Y. et al, where in the Kazakh population BMI, TG and TG/HDL levels correlated with HOMA-IR. The authors noted that Kazakh men were characterized by high levels of insulin sensitivity compared to Kazakh women (17).

In this study, a significant relationship between HOMA-IR groups and biochemical parameters was found with TG, apoB,

glucose and insulin levels. Hypertriglyceridemia increased the risk of IR by a factor of 2.59 and hyperpolypoproteinemia B by a factor of 1.74. Zheng S et al. investigated the relationship between the apoB/apoA1 ratio and the risk of developing type 2 DM (21). In another study looking for an association between MS components, a strong association of IR with apoB/apoA1 was found. The authors of this study recommend using apoB/apoA1 as a predictor of IR and for assessing CVD (19). Mao Y. reported a high apoB/apoA1 ratio was more common in patients with type 2 DM (20). This group of scientists concluded that the apoB/apoA1 ratio is closely related to TG, CHC, HDL, LDL, and high apoB/apoA1 ratios are associated with a risk of prediabetes and type 2 DM in women compared to men. Li X. et al. studied the relationship between apoB/ apoA1 ratio, IR and obstructive sleep apnea, their results showed that apoB/apoA1 ratio was associated with a risk of IR, they claimed that the higher the apoB/apoA1 ratio, the higher the risk of IR (22).

In conclusion, we found that in Kazakh women in our study, IR was more common than in Kazakh men, and IR was also

associated with apoB and TG levels. Thus, we can assume that analysis of TG level, apoB and apoB/apoA1 ratio can be recommended as early predictors of IR risk in Kazakh population. In the future, there may be studies in which the incidence of MS will be reduced based on the results obtained by controlling IR. These studies will result in improved quality of life in the development of interventions and strategies for the prevention and treatment of metabolic disorders in specific ethnic populations. Detection and analysis of a set of lipid metabolism indicators will improve early detection of IR in healthy individuals to choose the right tactics of lipid and carbohydrate metabolism correction as a timely prevention of DM and MS.

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Received February 19, 2023. Accepted March 7, 2023.