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Markers of Insulin Resistance in Patients with Different Extent of Atherosclerotic Lesions of Coronary Arteries

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Introduction

Atherosclerotic vascular disease remains the main cause of morbidity and mortality either in people with and without diabetes mellitus, which is especially important for Eastern European countries. Insulin resistance and/or hyperinsulinaemia can contribute to development and accelerate the progression of atherosclerotic damage of the large arteries [Laakso 2015]. However, an association between the severity of angiographically confirmed atherosclerotic lesions of coronary arteries and insulin resistance in patients with ischaemic heart disease (IHD) without history of diabetes mellitus or dysglycaemia was not properly examined. The aim of the study was to investigate the association of insulin resistance with the extent of atherosclerotic lesions of coronary arteries in patients with IHD.

Materials and methods

We examined 78 patients with clinical signs of IHD without history of diabetes mellitus or impaired glucose tolerance. Thirty patients had a history of myocardial infarction and 48 patients had angina pectoris. The mean age of patients enrolled was 61.5 ± 1.1 years, weight

87.9 ± 1.8 kg, height 1.73 ± 0.1 m, body mass index (BMI) 29.5 ± 0.6 kg/m² (data are presented here and everywhere as mean \pm SEM).

All patients studied underwent stress test, coronaroveniculography and oral glucose tolerance test. Blood



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was collected at fasting and 2 hours after glucose ingestion. Insulin levels were determined in all blood samples by ELISA along with plasma glucose measurements. Insulin sensitivity was characterised by the measurement of plasma insulin levels and calculation of HOMA-IR index, which is an established test for an estimation of insulin resistance [Matthews 1985]. HOMA-IR was calculated as fasting plasma glucose level (mmol/l) \times plasma insulin level (μ U/ml)/22,5. Only patients with angiographically confirmed lesions of coronary arteries were included in the study. The statistical analysis was performed with Student t-test and the difference between group was considered significant if $p < 0.05$.

Results

The patients were divided into the following groups for further analysis depending on the extent of atherosclerotic lesions of the coronary arteries: Group 1 – the atherosclerotic lesions were localized within 1 coronary artery, group 2 – there were stenotic lesions affecting 2 coronary arteries, and group 3 – the atherosclerotic lesions were angiographically detected in all arteries. There was no difference between the 3 groups of patients studied in age and BMI.

The levels of plasma glucose and insulin either at fasting or 2 hours after glucose ingestion, HbA_{1c} and HOMA-IR are presented in Table 1. HbA_{1c} and glucose levels at fasting and 2 hours after glucose load were not different between all 3 groups of patients studied. Fasting plasma insulin levels were significantly higher in patients with 2 or 3 damaged coronary arteries compared with those with 1 artery involved while there was no significant difference between groups 2 and 3. However, 2 hours after glucose administration plasma insulin levels were significantly higher in those subjects with the most severe atherosclerotic lesions compared with those with 1 or 2 coronary arteries involved into the atherosclerotic process. Moreover, those with 2 damaged coronary arteries had significantly higher insulin levels 2 hours after glucose intake compared with patients in group 1.

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HOMA-IR was higher than reference levels in all 3 groups of patients while it was statistically significant different between patients in group 3 compared with group 1.

Discussion

In our study we found that hyperinsulinaemia and elevation of HOMA-IR index as markers of insulin resistance are significantly related to more severe angiographically documented atherosclerotic lesions of coronary arteries in patients with IHD.

The patients enrolled in the study did not have a history of diabetes mellitus or dysglycaemia, which allowed the assessment of insulin production as the reflection of insulin sensitivity either at fasting or after glucose load along with

correlation between hyperinsulinaemia and increased lipid load of atherosclerotic plaque [Mitsuhashi 2011]. Insulin resistance was found to be associated with higher susceptibility of atherosclerotic plaque to thrombogenesis, which was characterised by thinner fibrotic cap, higher lipid content of the coronary plaque examined by optical coherent tomography in those subjects with severe insulin resistance [Iguchi 2014]. In patients with acute coronary syndrome insulin resistance was significantly associated with worse outcome and higher incidence of recurrence [Szepletowska 2015]. Insulin resistance was related to higher incidence of restenosis of coronary arteries in those subjects who underwent coronary stenting with the use of drug-eluting stents [Zhao 2015]. The association between greater extent of atherosclerotic lesions of coronary arte-

has the limitations that it is cross-sectional and that prospective observations would allow to assess more precisely the role of insulin resistance in the pathogenesis of coronary atherosclerosis.

We may conclude that hyperinsulinaemia and/or insulin resistance are associated with greater extent of angiographically confirmed atherosclerotic lesions of coronary arteries in patients with IHD. We may speculate that disturbances of insulin sensitivity can play a role in the progression of atherosclerosis of coronary arteries.

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Parameter	Group 1 (n=33)	Group 2 (n=24)	Group 3 (n=21)
HbA _{1c} (%)	5.96±0.13	5.7±0.10	5.80±0.14
Fasting plasma glucose (mmol/l)	6.31±0.21	5.78±0.15	5.74±0.26
Plasma glucose 2 hours after glucose ingestion (mmol/l)	8.15±0.60	8.56±0.47	7.26±0.61
Fasting plasma insulin (μ U/ml)	19.1±1.16	24.1±2.28 *	25.0±1.64 *
Plasma insulin 2 hours after glucose ingestion (μ U/ml)	35.3±2.38	65.2±4.33 *	79.85±2.81 *.*#
HOMA-IR	5.40±0.40	6.13±0.57	6.50±0.49 *

* p<0.05 compared with group 1, *#p<0.05 compared with group 2

Tab. 1: Characteristics of metabolic control and sensitivity to insulin in patients with ischaemic heart disease (IHD) and different extent of atherosclerosis of coronary arteries.

calculation of HOMA-IR index, which is considered the surrogate marker of insulin resistance [Matthews 1985].

IHD is the major cause of mortality in many eastern European and post-Soviet countries including Ukraine. Therefore, the assessment of the possible factors, which could underlie the progression of coronary atherosclerosis in our population of Ukrainian subjects with IHD, seems to be of importance. Earlier epidemiological studies showed that insulin resistance was associated with initiation and progression of coronary atherosclerosis in patients from the different ethnic groups [Patel 2016, Tunc 2017]. In a study of patients with coronary atherosclerosis employing intravascular ultrasound there was a strong

correlation between hyperinsulinaemia and increased lipid load of atherosclerotic plaque [Karrowi 2013]. In another series, the correlation between angiographically confirmed lesions of coronary arteries and insulin resistance was confirmed in patients with diabetes mellitus [Srinivasan 2013]. Experimental studies found that insulin can enhance the proliferation of smooth muscle cells of the arteries promoting atherogenesis [Breen 2011, Reddy 2010].

The strengths of our study are enrollment of a sufficient number of patients with IHD without any history of diabetes mellitus or dysglycaemia and the detailed angiographical examination of the coronary arteries. The study

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