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Early markers of atherosclerosis in patients with impaired fasting glucose

Wczesne markery miażdżycy u chorych z nieprawidłową glikemią na czczo

ABSTRACT

Introduction. It is known that increased plasma glucose, which includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes, is a risk factor for atherosclerosis. Individuals with IFG exhibit a higher rate of cardiovascular events compared with those with normal fasting glucose. The aim of the study was to evaluate whether IFG has an influence on early markers of atherosclerosis [intima media thickness (IMT), strain (S, deformation of the vessels wall), and strain rate (Sr, deformation over time)] in common carotid artery (CCA) compare to healthy subjects (without disturbances of glucose metabolism).

Patients and methods. A group of 25 dysglycemic patients with IFG and 15 healthy subjects of similar age and gender were examined. Blood analyses and anthropometric measurement [systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)] were obtained. Carotid IMT, S, and Sr were measured by tissue Doppler. IFP was diagnosed according to the diagnostic criteria for IFG in Poland.

Results. Patients with IFG had higher DBP and IMT of CCA (right and left) compared with control. There was no difference in SBP and HR between patients with IFG and controls. Strain of CCA was decreased in subject with IFG compared with controls and strain rate of CCA was increased in patients with IFG compared with the controls.

Conclusion. IFG may have an influence on early markers of atherosclerosis, but further investigations are needed to confirm these observations. (Diabet. Klin. 2015; 4, 1: 3–8)

Key words: atherosclerosis, prediabetes, impaired fasting glucose, intima media thickness

STRESZCZENIE

Wstęp. Podwyższone stężenie glukozy we krwi, obejmujące nieprawidłową glikemię na czczo (IFG), nietolerancję glukozy i cukrzycę, jest czynnikiem ryzyka miażdżycy. U pacjentów z nieprawidłową glikemią na czczo częstość występowania zdarzeń sercowo-naczyniowych jest większa niż u osób z prawidłową glikemią. Celem badania była ocena, czy IFG ma wpływ na wczesne markery miażdżycy: grubość kompleksu błony wewnętrznej (IMT), odkształcenie ściany naczynia (S) i odkształcenie w jednostce czasu (Sr) w tętnicach szyjnych wspólnych (CCA) w porównaniu z osobami zdrowymi (bez zaburzeń metabolizmu glukozy).

Pacjenci i metody. Zbadano 25 chorych z IFG oraz 15 zdrowych osób odpowiednio dobranych pod względem wieku i płci. Od chorych pobrano próbkę krwi oraz dokonano pomiarów skurczowego ciśnienia tętniczego (SBP), rozkurczowego ciśnienia tętniczego (DBP), częstości rytmu serca (HR). Oceny IMT tętnic szyjnych, S, Sr dokonano przy użyciu doplera tkankowego. Rozpoznania IFG dokonano na podstawie kryteriów rozpoznania obowiązujących w Polsce.

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Wyniki. Pacjenci z IFG mieli wyższe wartości DBP oraz IMT prawej i lewej CCA w porównaniu z grupą kontrolną. Nie stwierdzono różnicy między SBP i HR w grupie z IFG w porównaniu z grupą kontrolną. Odkształcenie ściany naczynia obu CCA było obniżone w grupie z IFG w porównaniu z grupą kontrolną, Sr był wyższy w grupie z IFG niż w grupie kontrolnej.
Wnioski. Nieprawidłowa glikemia na czczo może mieć wpływ na wczesne markery miażdżycy, jednak są potrzebne dalsze badania, by potwierdzić tę obserwację. (Diabet. Klin. 2015; 4, 1: 3–8)

Słowa kluczowe: miażdżyca, *prediabetes*, nieprawidłowa glikemia na czczo, grubość kompleksu błony wewnętrznej

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are described as prediabetes. Between 20% and 30% of patients with prediabetes will develop diabetes in the future. The risk of diabetes is increased when IFG coexists with IGT [1–3]. Both IFG and IGT are associated with increased risk of cardiovascular disease [4, 5]. Hyperglycemia is associated with arterial stiffness that incorporates arterial wall thickness, which may suggest that hyperglycemia is associated with altered material within the arterial wall. Elevated level of glucose is associated with the non-enzymatic glycation of proteins in skin, vasculature and lens collagen, and may promote collagen deposition, tissue inflammation and fibrosis [6]. In vitro studies have suggested that hyperglycemia affects the arterial wall by stimulating the proliferation of smooth muscle cells [7] and the non-enzymatic glycosylation of proteins [8].

American and European guidelines for the assessment of cardiovascular risk use a number of scales such as the Framingham Risk Score, Systematic Coronary Risk Evaluation (SCORE) and Reynolds Score [9–11], which are less useful when the cardiovascular risk is assessed individually. It is proven that assessment of same biomarkers such as intima media thickness is useful in the prediction of cardiovascular diseases.

Carotid intima media thickness (CIMT) is typically used to assess individual cardiovascular risk, because the atherosclerotic plaques commonly develop in a region near to the common carotid artery bifurcation. Moreover, it is easily accessible with ultrasound. It has been demonstrated that CIMT is an independent cardiovascular risk factor and the presence of the plaques in the carotid artery is a strong predictive factor of cardiovascular risk and mortality [12]. CIMT is also strongly positively associated with the risk for stroke [13]. Pyrzak et al. [14] revealed that atherosclerosis may have an onset in childhood and adolescence — ninety-one percent of obese children presented elevated CIMT which correlated with CRP (C-reactive protein).

Ultrasound B-mode examination can be used to assess the deformation of the carotid artery: *strain (S)* and changes of this deformation over time — *strain rate (Sr).*

Some investigators revealed that traditional cardiovascular risk factors are associated with increased CIMT in healthy individuals, as well as in patients with glucose metabolism disorders, and are predictive factors of coronary artery disease [15, 16]. Some studies note that sex, body mass and height may have an influence on CIMT. Mazurek et al. [17] assessed the intima media thickness (IMT) of the common carotid artery and the internal carotid artery (34 women and 29 men aged 20.2 ± 0.9 years). They revealed that IMT in both arteries was higher in women compared with IMT in men. There was also a positive correlation between body fat, height, body mass and IMT in women. There was an inverse relationship between IMT of the internal carotid artery and diastolic and systolic blood pressure in women. In men, there was a positive correlation between IMT and height, diastolic blood pressure and hsCRP (high sensitive C-reactive protein). Zhang et al. note a positive correlation between CIMT and waist circumference (a waist circumference greater than 90–95 cm was associated with higher CIMT) [18]. Some researchers report that a polymorphism in the apoB gene (apoB is one of the most important components of LDL, VLDL and IDL — atherogenic lipoproteins) is associated with increased CIMT [19]. Nikolajevic-Starcevic et al. report that polymorphism in the apoB gene (XbaI and EcoRI) is associated with higher prevalence of plaques in carotid artery but not with increased CIMT [19].

CIMT may be also useful in acute diseases such as Kawasaki disease. Wu et al. [20] report that CIMT is higher in Kawasaki disease than in acute infectious disease with syndromes similar to those of Kawasaki disease. Modern imaging modalities such as MRI may be useful in the assessment of the carotid artery. MRI has ability to image the entire circumference of the carotid wall, the outer wall of the carotid bulb where the plaque forms in its earliest stage, and identify plaque components such as the lipid core, fibrous cap, and intraplaque hemorrhage [21].

Aim of the study

The aim of the study was to determine whether impaired fasting glucose has an influence on early markers of atherosclerosis IMT, *S*, and *Sr* in the common carotid artery (CCA) compared with healthy subjects (without disturbances of glucose metabolism).

Materials and methods

Twenty-five dysglycemic patients with IFG (age ± standard deviation: 56 ± 5.3985) and 15 healthy subjects matched for age and gender were examined. The study was approved by local ethical committee. Blood analyses and anthropometric measurements [systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)] were performed. The CIMT, *S*, and *Sr* were measured as followed. Patient was examined in supine position after a rest of at least 5 minutes in a semi-dark room. The ECG trace was obtained and examinations were performed for both CCA using a Vivid 7 apparatus (GE Vingmed Ultrasound, Horten, Norway) with a 14 MHz linear transducer. The CIMT was semi-automatically assessed on long axis images of the CCA, about 1 cm below the carotid bulb. For the *S* and *Sr* analysis a cine loops of three cardiac cycles of the short axis were acquired in an arterial segment about 1cm below CCA bifurcation. Afterward they were analyzed on a workstation equipped with dedicated software (EchoPac PC, GE Medical System, Horten, Norway). Mean value of *S* and *Sr* for a 3 consecutive heart beats was included in analysis.

IFG was diagnosed according to the diagnostic criteria for IFG in Poland. Data were presented as a mean and $p < 0.05$ was considered significant. Student's T-test for independent samples was applied to assess the difference between the control and study groups for normally-distributed variables (IMT, S of the right CCA, SBP, DBP). The Mann-Whitney U-test was used to assess differences between the study and control groups when the variables were non-normally distributed (S of left CCA, *Sr* of left and right CCA).

Results

Patients with IFG had higher DBP compared with control (85.71 *vs.* 76.80, respectively, $p < 0.05$) (Tab. 1). No difference was observed in SBP between patients with IFG and controls (132.84 *vs.* 125.93 respectively $p > 0.05$) (Tab. 1) and HR between subjects with IFG and control (74.84 *vs.* 69.8 respectively, $p > 0.05$) (Tab. 2–4). Patients with IFG had greater carotid IMT than controls (left carotid IMT 0.6564 *vs.* 0.57 respectively, $p < 0.05$; right carotid IMT 0.5776 *vs.* 0.5017 respectively, $p < 0.05$) (Tab. 1). *Strain* in CCA was decreased in IFG subjects compared with controls (*strain* of left CCA — 3.1156 *vs.* 4.3093 respectively, $p < 0.05$,Tab. 2–4; *strain* of right CCA — 2.8596 *vs.* 4.4436 respectively, $p < 0.05$, Tab. 1) and *strain rate* of CCA was decreased in patients with IFG compared with controls (*strain rate* of right CCA — 0.499 *vs.* 0.6783 respectively, $p < 0.05$, Tab. 2–4; *strain rate* of left CCA — 0.446 *vs.* 0.6473 respectively, $p < 0.05$, Tab. 2–4).

Discusion

The early diagnosis and treatment of glucose metabolism disorders is one of the most important aims of Medicine. Ultrasound B-mode examination allows the detection and quantification of vascular disease and cardiovascular risk before any symptoms occur. Early detection of increased thickness may indicate the need for a more aggressive approach to managing the risk factors causally associated with heart disease and stroke. Numerous longitudinal studies indicate a linear relationship between both fasting and postprandial glucose concentrations and CVD. It is proven that hyperglycemia in diabetes is related to micro- and macrovascular complications. Rogowicz-Frontczak et al. revealed that in type 1 diabetic patients both CIMT and arterial stiffness were also related to age, blood pressure, kidney function and sICAM-1 serum concentration [22]. CIMT correlates also with features of metabolic syndrome in young people with a clinical diagnosis of familial hypercholesterolemia, without diabetes mellitus [23].

This risk extends to the non-diabetic range and is somewhat stronger for postprandial compared with

Table 1. Student's T test for study group (0) and control group (1). *Strain* of the right common carotid artery (Strain RCCA), systolic blood pressure (SBP), diastolic blood pressure (DBP), carotid intima media thickness of the left common carotid artery (IMTL), carotid intima media thickness of the right common carotid artery (IMTR)

Variable	Student's T-test: study group (0) and control group (1)								
	Mean (0)	Mean (1)	t	df	p	Number of important results (0)	Number of important results (1)	Standard deviation (0)	Standard deviation (1)
Strain RCCA	2.8596	4.4436	–3.78939	37	0.000539	25	14	1.01262	1.60308
SBP	132.84	125.933	1.16170	38	0.252603	25	15	18.3159	18.0097
DBP	85.720	76.8000	2.16643	38	0.036617	25	15	12.8501	12.1784
IMT L	0.6564	0.5700	2.25158	38	0.030211	25	15	0.11604	0.11994
IMT R	0.5776	0.5107	2.52997	38	0.015673	25	15	0.08594	0.07176

Table 2. Mann-Whitney U Test. *Strain* of the left common carotid artery (LCCA). heart rate (HR). *Strain rate* of the left common carotid artery (*Strain rate* LCCA). *Strain rate* of the right common carotid artery (*Strain rate* RCCA). (0 — study group, 1 — control group)

Group	IFG group		Control group		
Parameter	**Mean**	**SD**	**Mean**	**SD**	**p**
Strain LCCA (%)	3.12	1.48	4.31	1.29	0.0029
HR [1/min]	74.8	15	69.8	11	0.1988
Strain rate LCCA [1/s]	0.45	0.21	0.65	0.19	0.001
Strain rate RCCA [1/s]	0.49	0.13	0.68	0.20	0.0033

Table 3. Mann-Whitney U Test. *Strain* of the left common carotid artery (LCCA), heart rate (HR), *Strain rate* of the left common carotid artery (*Strain rate* LCCA), *Strain rate* of the right common carotid artery (*Strain rate* RCCA). (0 — study group, 1 — control group)

Variable	Mann-Whitney U-Test statistically significant results — p < 0.05					
	Sum of runks (0)	Sum of runks (1)	U	Z	p	N — number of important results — (0)
Strain LCCA	405.5000	414.5000	80.5000	–2.97531	0.002927	25
HR	559.0000	261.0000	141.0000	1.28511	0.198754	25
Strain rate LCCA	394.0000	426.0000	69.0000	–3.29659	0.000979	25
Strain rate RCCA	399.0000	381.0000	74.0000	–2.94234	0.003258	25

Table 4. Mann-Whitney U Test regard to variable. *Strain* of left common carotid artery (LCCA), heart rate (HR), *Strain rate* of the left common carotid artery (*Strain rate* LCCA), *Strain rate* of right common carotid artery (*Strain rate* RCCA). (0 — study group, 1 — control group)

Mann-Whitney U Test statistically significant results — p < 0.05		
Parameter	**Control group (number of important results) (1)**	**(1)*(0) p**
Strain LCCA	15	0.002106
HR	15	0.201329
Strain Rate LCCA	15	0.000611
Strain Rate RCCA	14	0.002470

fasting glucose concentrations. Impaired fasting glucose and IGT are associated with a modestly increased risk for CVD, but IGT may be a slightly better predictor. The coexistence of IFG and IGT is characterized by impairment in insulin secretion and increased hepatic activity [17–21, 24, 25]. However, there are some differences in the nature of the defects between the two conditions. Individuals with isolated IFG manifest normal to slightly-decreased insulin secretion and normal or slightly-impaired insulin action [24–30]. Isolated IGT is characterized by more severe muscle insulin resistance and less severe hepatic insulin resistance. While those with isolated IFG have defects in first-phase or early insulin secretion (in proportion to their fasting hyperglycemia), individuals with isolated IGT have more severe defects in second-phase or late insulin secretion. As might be expected, individuals with combined IFG/IGT manifest both hepatic and muscle insulin resistance as well as impairments in both first and second phase insulin secretion. Among subjects with prediabetes, those with combined IFG/IGT most closely resemble subjects with type 2 diabetes.

Most authors suggest that excessive hepatic glucose production is observed during IFG [30–32]. It is unknown whether IFG is linked with insulin resistance in the liver. Weyer et al. note that patients with isolated IFG or IFG and IGT demonstrate reduced suppression of glucose production induced by insulin [31]. In contrast, Perrault et al. report that in these conditions suppression of glucose production is not impaired [30]. It is known that morphological changes in blood vessels are greater in patients with IGT compared with those

with IFG. Aydin et al. [33] revealed that postprandial glucose level and HbA_{1c} have the most important influence on CIMT. They assessed 51 patients (22 with IFG, 29 with IGT) with a control group comprising 25 healthy individuals. The patients with ischemic heart disease, hypertension, hyperlipidemia, diabetes mellitus and thyroid disease were excluded. In both groups, fasting glucose, postprandial glucose, insulin concentration, insulin resistance and lipid concentration, CRP level, Hba_{1c} and microalbuminuria were assessed. CIMT was assessed using ultrasound Doppler examination. Both IFG and IGT patients have increased CIMT compared with controls. There was also a positive correlation between CIMT and fasting insulin concentration, postprandial glucose. HbA_{1c} level and insulin resistance described by HOMA (Homeostasis Model Assessment) in both control group and study group. There was the strongest correlation between CIMT and postprandial glucose level and HbA_{1c}.

In our study in patients with IFG CIMT was increased, *Strain* and *Strain rate* were worse compared to control. These results suggest that glucose metabolism disorders observed in prediabetes may have an influence on early structural and functional parameters of large blood vessels. However, the question is whether early intervention and proper treatment in prediabetes can reverse the structural and functional changes in blood vessels. Liu et al. [34] revealed that physical exercises may restore the function of the endothelium. Patients with IGT were found to demonstrate changes in concentration of endothelin-1, natriuretic peptides and ΔdiaP, OGTT (oral glucose tolerance test), adipose tissue, fasting insulin, HOMA and WHR (waist-hip ratio) due to physical exercises. There was no influence on CIMT and BMI (body mass index). These results suggest that physical exercise may improve endothelial function in patients with IGT and may prevent the development of diabetes. Further examinations are necessary to confirm whether lifestyle modification and pharmacological treatment in patients with IFG may prevent the development of cardiovascular diseases.

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