ORIGINAL PAPERS

Krzysztof Dębe[1], Mariusz Jasik[1], Sławomir Stawicki[2], Piotr Pacuła[1],
Waldemar Karnafel[1], Zygmunt Zdrojewicz[3]

The Effect of Aging on Glucose Tolerance and B Cell Secretion in Man

Wpływ wieku na tolerancję glukozy i czynność wydzielniczą komórek B wysp trzustkowych

[1] Department of Gastroenterology and Metabolic Diseases, University School of Medicine, Warsaw, Poland
[2] Department of Cardiology, University School of Medicine, Warsaw, Poland
[3] Department of Endocrinology and Diabetology, Wroclaw Medical University, Poland

Abstract

Objectives. The aim of the study was to evaluate the influence of aging on glucose tolerance, B cell secretion and hepatic clearance of insulin.
Material and Methods. 100 subjects of both sexes, aged between 17 and 92, of BMI < 27 kg/m^2 were studied. All subjects were divided into 4 groups according to their age: 18 patients aged 17–59 (group I – mean age 46 ± 12 (SD) years), 23 patients aged 60–69 (group II – mean age 64 ± 3 years), 33 patients aged 70–79 (group III – mean age 75 ± 3 years), and 26 patients aged 80–92 (group IV – mean age 84 ± 4 years). The oral glucose tolerance test (OGTT 75 g) and the intravenous glucagon test (IGT 1 mg) were carried out and blood glucose, serum insulin (IRI) and C-peptide (CP) were measured in all participants. Hepatic clearance of insulin was calculated on the basis of serum CP/IRI ratio.
Results. In the older groups the increase of fasting glycaemia and glycaemia levels after applied stimuli were observed (4.25 ± 0.6 vs. 4.7 ± 0.5 mM, group I vs. group IV respectively, p = 0.02). Similarly, the decrease of fasting and after OGTT and IGT CP levels in serum was found (OGTT 0.6 ± 0.2 vs. 0.35 ± 0.13 nM, group I *vs.* group IV respectively, p < 0.05). There was no difference in serum IRI concentrations.
Conclusions. Consequently, the serum CP/IRI ratio decreased from 10 ± 3.8 in group I to 5.4 ± 1.7 in group IV (p < 0.05) and showed reduced insulin clearance in liver, probably as a compensatory adaptation to the deterioration of B cell secretion (**Adv Clin Exp Med 2004, 13, 4, 595–600**).

Key words: glucose tolerance, serum insulin, serum C-peptide, aging.

Streszczenie

Cel pracy. Celem pracy była ocena tolerancji glukozy, czynności wydzielniczej komórek B wysp trzustkowych oraz klirensu wątrobowego insuliny w różnych grupach wiekowych.
Materiał i metody. Do badań zakwalifikowano 100 zdrowych osób w wieku 17–92 lat, ze wskaźnikiem masy ciała (BMI) < 27 kg/m^2, które zostały podzielone na 4 grupy wiekowe: I grupa licząca 19 osób w wieku 17–59 lat (średnia 45,74 ± 11,84 (SD) lat), II grupa licząca 23 osoby w wieku 60–69 lat (średnia 64,13 ± 3,28 lat), III grupa – 33 osoby w wieku 70–79 lat (średnia 74,82 ± 3,16 lat), IV grupa – 26 osób w wieku 80–92 lat (średnia wieku 84 ± 3,58 lat). Oznaczono glikemię oraz stężenie peptydu C (CP) i insuliny (IRI) w surowicy w trakcie doustnego obciążenia glukozą (OGTT) oraz po dożylnym wstrzyknięciu glukagonu. Klirens wątrobowy insuliny oceniano z wartości stosunku molarnego CP/IRI w surowicy krwi obwodowej na czczo oraz w poszczególnych punktach czasowych w obu testach.
Wyniki. W starszych grupach wiekowych stwierdzono wzrost wartości glikemii na czczo (I grupa 4,25 ± 0,61; IV grupa 4,66 ± 0,47 mM; p = 0,02) oraz w obu testach zmniejszenie podstawowego stężenia peptydu C (I grupa 0,58 ± 0,19; IV grupa 0,35 ± 0,13 mM; p < 0,05) i stężenia peptydu C po stymulacji przy niezmieniającym się stężeniu insuliny (IRI) we krwi pozawątrobowej.
Wnioski. Nastąpiło obniżenie stosunku molarnego peptydu C do insuliny (I grupa: CP/IRI podstawowe 10,1 ± 3,8; IV grupa: CP/IRI 5,4 ± 1,7; p < 0,05), co dowodzi zmniejszonego pobierania insuliny przez wątrobę i może być reakcją kompensacyjną na upośledzoną czynność komórek B wysp trzustkowych (**Adv Clin Exp Med 2004, 13, 4, 595–600**).

Słowa kluczowe: tolerancja glukozy, insulina w surowicy, peptyd C w surowicy, wiek.

Assessment of the carbohydrate metabolism and the secretion of B cell during the process of aging attracted a lot of interest among explorers over the past decades [1–3]. It is generally assumed that aging has an important impact on metabolism including the carbohydrate metabolism. In older people atherosclerotic changes in pancreatic arteries and degenerative processes, e.g. amyloid depletion, occur more frequently.

Pancreatic gland mass is diminished up to 50% [4]. A significant reduction in number of B cells in comparison with the amount of A cells in pancreas was also noticed.

The impact of age on changes in concentration of insulin in post-hepatic blood remains controversial. The aim of this work was to assess the secretion of B cells based on measurements of insulin and C peptide in serum in different age groups.

Material and Methods

100 patients who fulfilled the following criteria were included: negative family history of diabetes mellitus, no history of liver, pancreas and kidney disease, the absence of any inflammatory processes or disorders affecting carbohydrate metabolism, fasting capillary blood glucose < 100 mg/dl and < 140 mg/dl in the 2nd hour of oral glucose tolerance test (75 g of glucose), level of glycated haemoglobin < 7.5% and fructosamine < 2 mmol/l, body mass index (BMI) < 27 kg/m^2 and >18 kg/m^2, waist to hip ratio (WHR) < 0.9 for men and < 0.8 for women. Patients were not allowed to take any medication affecting secretion and liver clearance of insulin, as well as metabolism of glucose. A characteristic of the study group is shown in Table 1.

All patients underwent oral glucose tolerance test (75 g of glucose) with blood samples taken in fasting state and in the 30th, 60th and 120th minute of the test. After 7 days a glucagon test (1 mg of glucagon i.v.) with blood glucose taken in fasting state and in the 5th, 15th, 30th, 45th, 60th minute was performed. Glycaemia, insulin concentrations in serum and C peptide were determined using enzymatic method of Cormay GS-120L kit, RIA method (double antibodies RIA-IRI-ORIPI), and RIA method (Byk-Mallinckrodta kit) respectively. For every sample C peptide to insulin ratio was calculated (CP/IRI) in order to reflect liver clearance of insulin. For every age group the average values of glycaemia, serum insulin (IRI), and serum C peptide at all time points of the performed tests, average maximal values of glycaemia, serum insulin (IRI), serum C peptide, average increases

Table 1. Study groups

Tabela 1. Grupy badane

Study Groups (Grupa badana)	Number (Liczba)	Age – years (Wiek – lata)	BMI – kg/m^2; x ± SD (Wskaźnik masy ciała – kg/m^2)
Group I (Grupa I)	18	45.72 ± 11.84 (17–59)	23.99 ± 2.56
Women (Kobiety)	12	45.83 ± 12.16	23.8 ± 2.92
Men (Mężczyźni)	6	45.5 ± 12.29	24.37 ±1.8
Group II (Grupa II)	23	64.13 ± 3.28 (60–69)	25.55 ± 1.95
Women (Kobiety)	18	64.5 ± 3.49	25.61 ± 1.94
Men (Mężczyźni)	5	62.8 ± 2.17	25.32 ± 2.2
Group III (Grupa III)	33	74.82 ± 3.16 (70–79)	25.15 ± 1.99
Women (Kobiety)	26	75.08 ± 3.02	25.16 ± 2.05
Men (Mężczyźni)	7	73.86 ± 3.72	25.11 ± 1.94
Group IV (Grupa IV)	26	84 ± 3,58 (80–92)	23.84 ± 2.49
Women (Kobiety)	17	83 ± 3.16	23.74 ± 2.68
Men (Mężczyźni)	9	85.89 ± 3.72	24.64 ± 2.21

of these values and areas under the curve (AUC) as well as CP/IRI ratios were calculated.

In statistical analysis *t*-Student test was used and p < 0.05 was accepted as a significant level.

Results

Average levels of glycaemia, serum insulin, serum C peptide and CP/IRI ratio for each group in two tests are presented on Figures 1–3.

Group II versus Group I

The levels of glycaemia in fasting state, after oral charge and after injection of glucagon were higher in group II than in group I. Basic insulin concentration in serum, maximal level and the increase of secretion did not differ significantly. Basic and maximal concentration of C peptide in serum and CP/IRI ratio in both tests were slightly lower. However, these differences were not statistically significant. Area under curve for glycaemia, insulinaemia and C peptide did not differ significantly in both tests.

Group III versus Group I

The level of fasting glycaemia was slightly higher in group III than in group I, but did not reach statistical level. The average maximal level of glycaemia during OGTT was significantly higher, and the increase of glycaemia level was also slightly higher, however not statistically different. The increase of maximal glycaemia level and the slightly higher increment of glycaemia (without statistical significance) after intravenous injection of glucagon were noted. There were no significant differences in basic and maximal levels and in increment of insulin level in serum. There was also a significant decrease in basic C peptide concentration in serum and decrease of its maximal level and smaller increase of secretion of this peptide in both dynamic tests. The ratio of serum CP/IRI was lower. The AUC for glycaemia during OGTT and glucagon test were greater than in group I. The areas under the curve for both insulin and C peptide during OGTT and glucagon test were smaller, however, they were not statistically significant.

Group IV versus Group I

The highest average values of fasting and maximal glycaemia in both tests were observed in group IV. These differences were significant in comparison to group I. The increment of glycaemia was greater but significant only for glucagon test.

The basic and maximal insulin levels, and the increment of secretion did not differ.

The lowest basic and maximal C peptide concentrations in serum were observed in group IV. In this group the most pronounced increase in C peptide secretion during OGTT and glucagon test were noted. These values reached the level of significance even in comparison with group III. In this group the lowest value of CP/IRI ratio in serum was observed. AUCs of glycaemia in both tests were greater, AUC of insulin in serum did not differ while AUC of C peptide was significantly smaller in comparison with group I.

A significant positive correlation between age and: fasting glycaemia (r = 0.23, p = 0.02), maximal glycaemia in glucagon test (r = 0.27, p = 0.01) and during OGTT (r = 0.32, p = 0.001), increment of glycaemia in glucagon test (r = 0.39, p = 0.0001) were observed in the analysis of regression. There was a negative correlation between age and: basic C peptide concentration (r = –0.39, p = 0.0001), maximal C peptide values, its increment after both stimuli, and CP/IRI ratio in serum at each point with the exception of value in the 45th minute of the glucagon test.

There was no correlation between age and the basic insulin concentration in serum, the increase of secretion, the maximal secretion after oral stimulus, and in other time points of both dynamic tests with the exception of the 5th minute of glucagon test and increase of secretion in the glucagon test.

Positive correlation between age and: AUC of glycaemia in both dynamic tests (r = 0.302, p = = 0.0023), and a negative correlation between age and AUC of C peptide (r = –0.292, p = 0.003) were noted. There was neither correlation between age and AUC of insulin during OGTT nor in the glucagon test.

Discussion

Insulin and C peptide are secreted into bloodstream in equimolar quantities, but only the C peptide passes almost entirely through the liver and its degradation takes place mostly in kidneys. It has about 3-times longer half-time period and its concentration in posthepatic blood is several times higher than the concentration of insulin [5]. Therefore C peptide concentration in systemic blood is a measure of B cell secretion.

Calculation of CP/IRI molar ratio in posthepatic blood enables to assess the rate of hepatic insulin clearance [6].

The results have shown the gradual increase of fasting glycaemia, glycaemia after oral load of glucose and after intravenous glucagon, but

glycaemia (mmol/l)
glikemia (mmol/l)

a

glycaemia (mmol/l)
glikemia (mmol/l)

a

insulin in serum (nmol/l)
insulina w surowicy (nmol/l)

b

insulin in serum (nmol/l)
insulina w surowicy (nmol/l)

b

C peptide in serum (nmol/l)
peptyd C w surowicy (nmol/l)

c

C peptide in serum (nmol/l)
peptyd C w surowicy (nmol/l)

c
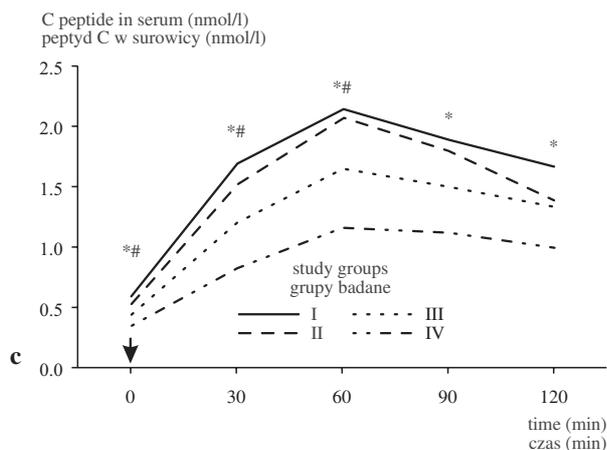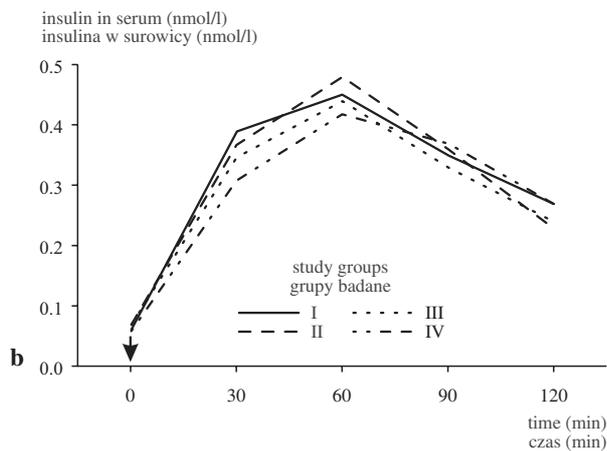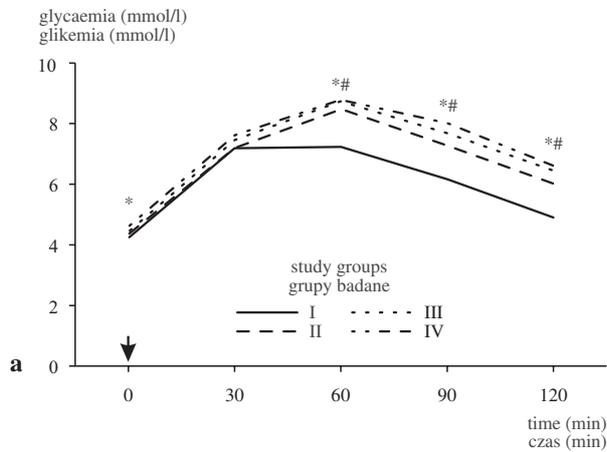
Fig. 1. a – Mean blood glucose during oral glucose tolerance test: * p < 0.05 between groups I and IV, # p < 0,05 between groups I and III; **b** – mean insulin concentrations in serum during oral glucose tolerance test; **c** – mean C-peptide concentrations in serum during oral glucose tolerance test: * p < 0.05 between groups I and IV, # p < 0.05 between groups I and III

Ryc. 1. a – Średnie wartości glikemii po doustnym obciążeniu glukozą:* p < 0,05 między grupą I i IV, # p < 0,05 między grupą I i III; **b** – średnie wartości stężenia insuliny (IRI) po doustnym obciążeniu glukozą; **c** – średnie wartości stężenia peptydu C w surowicy po doustnym obciążeniu glukozą: * p < 0,05 między grupą I i IV, # p < 0,05 między grupą I i III
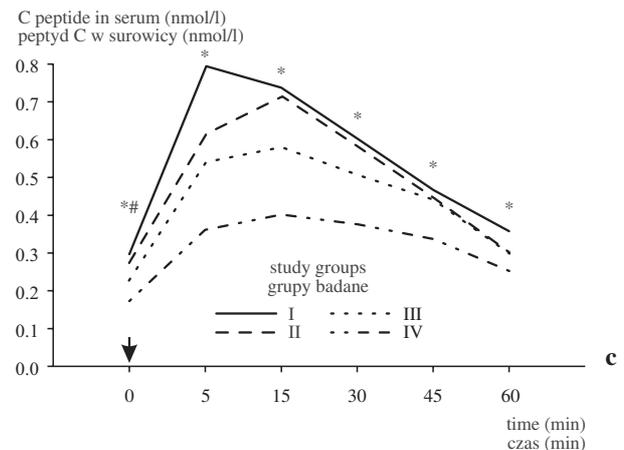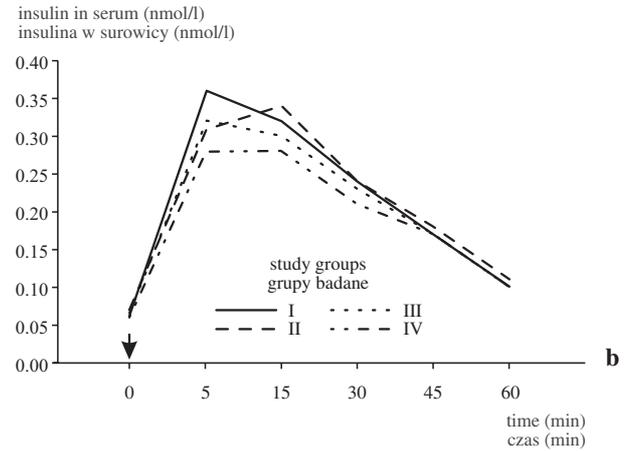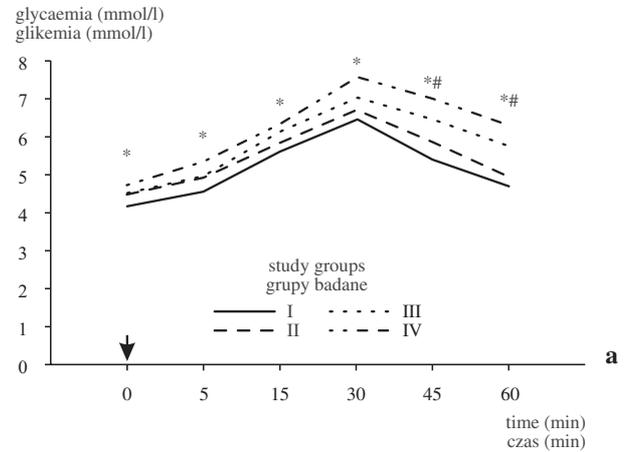
Fig. 2. a – Mean blood glucose after intravenous administration of glucagon: * p < 0.05 between groups I and IV, # p < 0.05 between groups I and III; **b** – mean insulin concentrations in serum after intravenous administration of glucagon; **c** – mean C-peptide concentrations in serum after intravenous administration of glucagon: * p < 0.05 between groups I and IV, # p < 0.05 between groups I and III

Ryc. 2. a – Średnie wartości glikemii po dożylnym obciążeniu glukagonem.* p < 0,05 między grupą I i IV: # p < 0,05 między grupą I i III; **b** – średnie wartości stężenia insuliny (IRI) po dożylnym obciążeniu glukagonem; **c** – średnie wartości stężenia peptydu C w surowicy po dożylnym obciążeniu glukagonem: * p < 0,05 między grupą I i IV, # p < 0,05 między grupą I i III
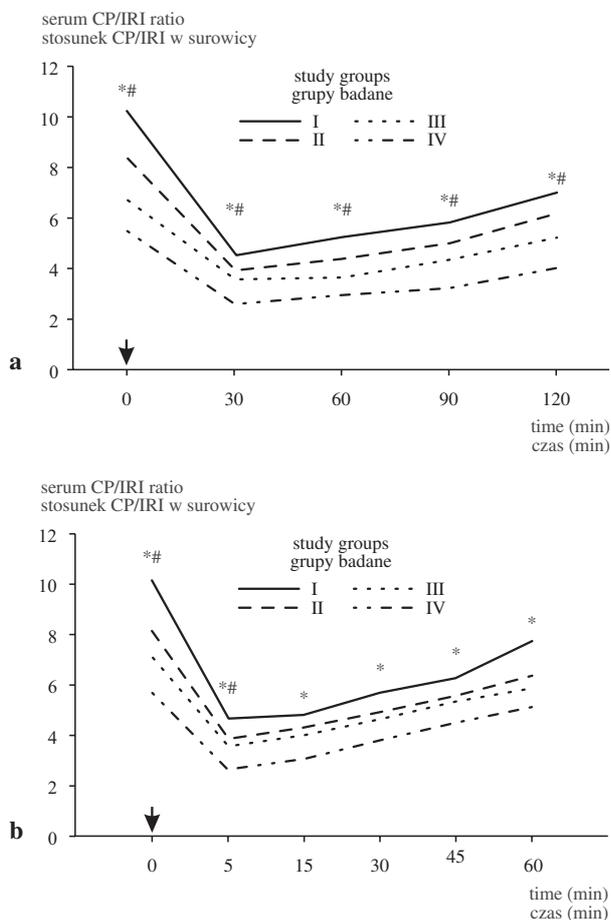
Fig. 3. a – Mean values of CP/IRI ratio during oral glucose tolerance test: * p < 0.05 between groups I and IV, # p < 0.05 between groups I and III; **b** – mean values of CP/IRI ratio after intravenous administration of glucagon: * p < 0.05 between groups I and IV, # p < 0.05 between groups I and III

Ryc. 3. a – Średnie wartości stosunku molowego CP/IRI po doustnym obciążeniu glukozą: * p < 0,05 między grupą I i IV, # p < 0,05 między grupą I i III; **b** – średnie wartości stosunku molowego CP/IRI po dożylnym obciążeniu glukagonem: * p < 0,05 między grupą I i IV, # p < 0,05 między grupą I i III

a decrease in basic and stimulated concentrations of C peptide in serum in the course of aging. These data have proved the process of progressive deterioration of B cells function without accompanying changes in basal and maximal insulin concentration in serum and its increment in both tests. A considerable decrease of CP/IRI ratio in older groups indicates the decline in hepatic clearance of insulin. It is probably the result of a reduction of active liver cells caused by aging. However, it is known that the presence of about 20% cells of liver is sufficient to maintain the normal carbohydrate homeostasis [4, 7]. After intravenous administration of glucagon, the maximal values of glycaemia were significantly higher in older subjects, suggesting normal glycogenolysis activity of glucagon in the liver. These data support the hypothesis that diminished clearance of insulin in liver compensates deterioration of B cell secretion. The presence of higher fasting and stimulated glycaemia levels in older groups and unchanged insulin concentrations in post-hepatic blood may indicate the gradual development of insulin resistance (on receptor or post-receptor level) during aging processes. Several mechanisms may contribute to such resistance: diminished number of insulin receptors, decreased activity of tyrosine kinase in beta subunit of insulin receptor, reduced number and activity of glucose transporters GLUT 4 in muscles, adipocytes and fibroblasts [8–11]. On the other hand a rise in proinsulin quantity is also possible, but proinsulin is not detectable in routine tests due to cross reaction with insulin antibodies [8].

The rise in fasting glycaemia levels in older groups may result from increased hepatic glucose production in course of glycogenolysis and gluconeogenesis [12–16]. In older people there is a marked decrease in muscle mass and physical activities, that results in reduction of the utilization of glucose in tissues [17–21].

The postulated role of amylin and the similar calcitonin gene related peptide (CGRP) in the process of aging remains unclear [22]. The long-term hyperglycaemia observed in older people may be responsible for glucotoxic effect and the enhanced negative impact on insulin secretion in B cells. This may lead to greater peripheral insulin resistance, probably through down regulation of glucose transporters and possible disturbances of intracellular transport of glucose [23–26].

A significant increase in fasting glycaemia as well as after oral load of glucose and intravenous stimulation by glucagon is characteristic of the aging.

B cell dysfunction in older groups manifested by a diminished mean C peptide concentration in serum in fasting state, and after stimulation of glucose and glucagon.

During the process of aging a decrease in serum CP/IRI ratio was observed, indicating reduction of liver clearance of insulin as a compensation for B cell dysfunction.

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Address for correspondence:

Krzysztof Dęmbe
Department of Gastroenterology and Metabolic Diseases
University School of Medicine in Warsaw
Banacha 1a
02-097 Warsaw