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Assessment of preservation of beta-cell function in children with long-standing type 1 diabetes with „ultrasensitive c-peptide" method

Ocena zachowania funkcji komórek beta trzustki u dzieci z długotrwającą cukrzycą typu 1 z użyciem ultraczułej metody oznaczania c-peptydu

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Abstract

Introduction. Type 1 diabetes mellitus is a disease caused by the autoimmune destruction of pancreatic beta-cells. It was previously believed that the loss of the endocrine function of the pancreas is total and inevitable. With the rise of new knowledge and new methods allowing to reliably measure c-peptide in the low plasma concentration range, we have learned otherwise. Some residual function of the beta-cells can be present even after decades of the course of the disease. **The aim of** the study was to evaluate the c-peptide level with routine laboratory and ultrasensitive methods in children with long-standing type 1 diabetes in relation to clinical characteristics. **Methods.** We recruited 178 consecutive children with type 1 diabetes mellitus lasting at least 1 year, mean diabetes duration was 5.6 years. Basic anthropometric measurements were performed and blood samples were drawn. From patients history records we gathered data regarding the course of the disease and laboratory results previously acquired. Laboratory tests performed on the blood samples included HbA_1c levels and c-peptide level measurement using classic (n=178) and ultrasensitive (n=160) method (Mercodia). Clinically relevant c-peptide level was set at 0.23 ng/ml according to the DCCT recommendations. **Results**. Clinically relevant c-peptide was found in 54 of 160 (33.75%) patients. Patients with preserved c-peptide were older at the time of diagnosis, had longer clinical remission, and required lower total and basal doses of insulin. Significantly lower mean HbA_1c from the last year, but higher HbA_1c at the time of the diabetes diagnosis were found in the group with higher c-peptide levels. The comparison of the classic and ultrasensitive c-peptide tests revealed that both yield similar results. **Conclusions**. Our observation shows that 34% of young patients with long-standing type 1 diabetes have prolonged c-peptide secretion. We confirm the long-standing assumption that residual beta-cell function is beneficial for metabolic control of the patients. Classic method of the c-peptide measurement can be just as useful in clinical practice as the ultrasensitive one.

Key words
ultrasensitive c-peptide, long standing type 1 diabetes , children

Streszczenie

Wstęp. Cukrzyca typu 1 jest autoimmunizacyjną chorobą, w której zniszczeniu ulegają komórki beta wysp trzustkowych. Jeszcze do niedawna sądzono, że utrata wewnątrzwydzielniczej funkcji trzustki jest całkowita i nieunikniona. Jednak wraz z rozwojem wiedzy oraz powstaniem nowych wiarygodnych metod oznaczania c-peptydu przy jego bardzo niskich stężeniach okazało się, że szczątkowa funkcja gruczołu może być zachowana nawet dekady od diagnozy. **Celem badania** była ocena stężenia c-peptydu za pomocą rutynowej metody laboratoryjnej oraz nowej metody ultraczułej u dzieci z długotrwającą cukrzycą typu 1 w relacji do charakterystyki klinicznej pacjentów. **Metody.** Do badania włączyliśmy 178 kolejnych pacjentów z cukrzycą typu 1 trwającą co najmniej 1 rok, średni czas trwania cukrzycy wynosił 5,6 lat. Zostały wykonane podstawowe pomiary antropometryczne oraz pobrane próbki krwi. Z medycznych historii pacjentów zebrano informacje dotyczące przebiegu choroby i wcześniejszych wyników

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laboratoryjnych. W pobranych próbkach krwi oznaczono wartość HbA_1c oraz stężenie c-peptydu metodą klasyczną (n=178) i ultraczułą (n=160) (Mercodia). Klinicznie istotne stężenie c-peptydu uznano przy wartości 0,23 ng/ml zgodnie z rekomendacjami DCCT. **Wyniki.** Klinicznie istotne stężenie c-peptydu stwierdzono u 54 z 160 pacjentów (33,75%). Pacjenci z zachowanym stężeniem c-peptydu byli starsi w czasie diagnozy, mieli dłuższy okres remisji i wymagali mniejszych całkowitych i bazalnych dawek insuliny. W grupie z zachowanym wydzielaniem c-peptydu stwierdzono istotnie niższą średnią wartość HbA_1c z ostatniego roku i wyższą wartość HbA_1c w momencie diagnozy choroby. Porównując klasyczną i ultraczułą metodę oznaczania c-peptydu, uzyskaliśmy podobne wyniki. **Wnioski.** Wykazano zachowane wydzielanie c-peptydu u 34% dzieci z długotrwająca cukrzycą typu 1. Nasze obserwacje potwierdzają przypuszczenie, że szczątkowa funkcja komórek beta wysp trzustki (mierzona stężeniem c-peptydu) jest korzystna dla wyrównania metabolicznego pacjentów. Klasyczna metoda oznaczania stężenia c-peptydu może być równie przydatna w praktyce klinicznej, jak metoda ultraczuła.

Słowa kluczowe
c-peptyd metoda ultraczuła**,** długotrwająca cukrzyca typu 1, dzieci

Introduction

Type 1 diabetes mellitus is characterized by an autoimmune reaction against beta-cells. It results in gradual decline in the endocrine function of the pancreas, and what follows – impaired metabolism of glucose. The process is heterogeneous and of variable dynamics, and can take from a month to years [1]. Between first clinical manifestation and complete loss of beta-cell function of the pancreas a period of remission, at least partial, occurs in majority, although not in all patients. This period is characterised by low insulin demand (<0,5 U/kg of body weight) usually accompanied by excellent metabolic control. A few decades ago it was believed that total destruction of the beta-cells, once started, is inevitable, which belief was implied by growing need for insulin [2]. Now we know that some beta-cells may remain and be still functional, even after decades of the course of the disease [3–5]. Moreover, it was noticed that even very small, residual endocrine function correlates with fewer long term complications, lower risk of severe hypoglycaemia, as well as better metabolic control [6]. Clinically relevant levels of c-peptide that are believed to be significant enough to benefit the patient are not yet clearly determined. Although most common assumption is that 0.23ng/ml is a cut-off value [7], some publications mention levels as low as 10 pmol/l [8]. It was proved that such patients suffered less severe hypoglycaemia and had less chronic complications [7,8]. Rise of the research addressing the problem of residual c-peptide levels started with the introduction of new ultrasensitive tests. Available new tests can measure the c-peptide level with the detection limit as low 1.5 pmol/L [5].

Nowadays, intense effort is put into searching for factors predisposing to long term beta-cell survival [9–11]. It needs to be answered what patients are predisposed to retain some of endocrine function of the pancreas for long period of time, and if anything can be done to preserve it. Knowing clinical, metabolic and genetic characteristic of patients retaining the beta-cells function would be beneficial from both diagnostic and therapeutic standpoint. It can be done by analyzing clinical data of the patients that retained higher levels of c-peptide and comparing it with the data of the patients with low c-peptide levels.

In the present study, we aimed to examine c-peptide level in young patients with long-lasting type 1 diabetes with use of traditional and new "ultrasensitive" methods. We wanted to check if there are any significant differences between patients secreting clinically significant amount of c-peptide and patients secreting less than this. Pediatric population provides us with unique opportunity to examine, as the differences between these groups can be seen at the very beginning of the disease. In the scope of our study we examined pediatric patients suffering from diabetes type 1 for longer than one year, assuming that it is the typical time for the ending of remission period. We hoped it can give us unique insight into factors affecting patients at the early, perhaps crucial period of the disease. We tried to establish if there are any protective factors if it comes to long term beta-cell survival, or any trait that would foretell the rapid decline of their function.

Research design and methods

Patients

For the study, we recruited 178 consecutive patients hospitalized in the Clinic between 2015 and 2017 due to previously diagnosed type 1 diabetes mellitus, according to the ISPAD criteria [12]. The disease was diagnosed in accordance with the guidelines, by clinical manifestation, high serum glucose and the presence of autoantibodies characteristic oftype 1 diabetes mellitus (ICA, IAA and anti-GAD) [12]. All of them were treated with multiple daily injection of insulin or continuous subcutaneous insulin infusion. From patients' history records we gathered data about the age at the time of the of diagnosis, duration of the disease, HbA_1c levels at the diagnosis and current (mean value from the last year, that was average from three or four measurements taken every three months), body mass index (BMI) at the time of diagnosis and currenty, the duration of clinical remission. Main inclusion criterion for the study was the duration of the type 1 diabetes mellitus longer than 1 year.

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Methods

Clinically significant c-peptide level was established at 0.23ng/ml as assessed by ultrasensitive c-peptide assay. Patients were further categorized into group 1 (patients with clinically significant preserved c-peptide) or group 2 (patients without preserved c-peptide). We also assessed our patient in dependence on optimal glycemic control understood as $HbA_1c < 7.5\%$ vs suboptimal glycemic control understood as $HbA_1c \geq 7.5\ \%$) [13].

Basic physical examination was performed and blood samples were taken. All children underwent physical examination, height and weight were taken in a standard way using Harpenden stadiometer and digital scale (Seca, Germany). BMI (body mass index) and SDS BMI (standard deviation score of BMI, according to formula: SDS-BMI= (BMI current – BMI 50 centile)/ 0,5 (BMI 50 centile – BMI 3 centile)) were calculated with standard formulas, using the results of OLAF study for Polish children [14].

Laboratory investigations

Blood sample of 5 mL was taken from the left cubital vein, after an overnight (8-12 hr) fast. In our study, we used c-peptide as a marker of maintaining pancreatic endocrine function, for it is secreted in equimolar proportion with insulin. We measured its levels using a traditional laboratory test. Then, 160 of the patients were randomly selected and their c-peptide levels were additionally measured using ultrasensitive method c-peptide ELISA (Mercodia, Sylveniusgatanm, Sweden) using ELx 800 Automated Microplate Reader, Bio-Tek Instruments, Vermont,

Table I. General characteristics of the study group
Tabela I. *Ogólna charakterystyka badanej grupy*

Study group/ Grupa badana		
Age (years)/ wiek (lata)	12.8 ± 3.5	n = 178
Age at the time of diagnosis (years)/ wiek w czasie diagnozy choroby (lata)	7.3 ± 3.8	n = 178
Duration of the disease (years)/ Czas trwania choroby (lata)	5.6 ± 3.8	n = 178
Mean HbA_1c from the last year (%)/ Średnia HbA_1c z ostatniego roku(%)	7.78 ± 1.19	n = 178
HbA_1c at the time of diagnosis (%)/ HbA_1c z okresu badania (%)	10.27 ± 2.16	n = 153
Height (cm)/ wzrost (cm)	154.6 ± 18.7	n = 178
Weight (kg)/ masa ciała (kg)	49.9 ± 17.9	n = 178
Current BMI (kg/m^2)/ aktualne BMI	20.1 ± 3.6	n = 178
Current/ aktualne SDS BMI	0.59 ± 1.04	n = 178
BMI at the time of diagnosis (kg/m^2)/ BMI z czasu diagnozy choroby	15.9 ± 2.9	n = 158
SDS BMI at the time of diagnosis/ SDS BMI z okresu diagnozy choroby	-0.29 ± 1.11	n = 151
Remission duration (months)/ Czas remisji (miesiące)	6.9 ± 7.5	n = 165
Total insulin dose (U/kg/24h) Całkowita dawka insuliny	0.77 ± 0.20	n = 178
Basal insulin dose (U/24h)/ Podstawowa dawka insuliny	13.1 ± 6.54	n = 178
Bolus insulin dose (U/24h)/ Dawka insuliny na bolusy	25.8 ± 12.68	n = 178
Classic c-peptide level (mg/dl)/ c-peptyd metodą klasyczną	0.02 (0.01-0.16)	n = 178
Ultrasensitive c-peptide level (ng/ml)/ c-peptyd metodą ultrasensitive	0.07 (0.0076-0.35)	n = 160

Data represented as mean ± standard deviation or median (interquartile range).
Dane przedstawione są jako średnia±odchylenie standardowe lub mediana (rozstęp kwartylowy).

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USA. Detection limit of the method used in our study is < 2.5 pmol/lthat corresponds to 0,0076 ng/ml (manuals form the manufacturer of the test: Mercodia). HbA_1c was evaluated with use of monoclonal antibodies in a biochemical analyzer (Cobas, Integra 800, Roche, Switzerland).

Statistical analysis

Statistical analysis was performed using the Statistica 12.00 software (StatSoft, Kraków, Poland). The Kolmogorov-Smirnov test of normality was used to test the distribution of variables. For normally distributed variables, the unpaired student t-test was used and for not normally distributed variables the Mann-Whitney U-test was used to compare the differences between the two groups. Relations between variables of interest were assessed by Pearson's correlation coefficient for parametric and Spearman's rank coefficient for nonparametric data. In order to detect independent determinants of c-peptide multiple linear regression analysis was performed. All data are expressed as either mean±SD or medians (interquartile range). Statistical significance was determined at $P<0.05$ level.

The approval of the Ethical Committee in the Medical University of Białystok was obtained. Both parents/legal guardians and children gave their written informed consent.

Results

We examined 178 patients suffering from type 1 diabetes mellitus for at least 1 year. The characteristics of the group is shown in Table I. Average age was 12.87 years, disease duration was 5.57 years, HbA_1c at the time of diagnosis was 10.27 % and mean HbA_1c from last year was 7.78%, remission duration was 6.87 months. Mean doses of insulin were 0.77 U/ kg of body weight/day.

160 of the patients were randomly selected and their c-peptide levels were measured using the ultrasensitive method. Clinically relevant c-peptide (>0.23 ng/ml) was found in 54 of 160 (33.75%) patients. Average age of children in both groups was the same, but patients with higher c-peptide were older at the time of diagnosis (10.05 vs 6.13 yrs, $p < 0.01$). Patients in group 1 had been suffering from diabetes mellitus for shorter time than patients in group 2. The duration of clinical remission was significantly longer in the group with significant c-peptide level (10.86 vs 5.25 months, $p < 0.01$). Patients in group 1 at the time of diagnosis had higher BMI SDS than the patients in group 2 (-0.005 vs -0.505, $p < 0.01$), however no such difference was found in current BMI SDS. Higher total (0.71 vs 0.8 U/kg, $p = 0.01$) and basal (10.76 vs 13.91 U, $p < 0.01$) insulin doses were required by patients in group 2 than group 1 (Table II). Effectiveness of the treatment measured by average glycated hemoglobin during the last year proved better metabolic control in group with higher c-peptide (7.24 vs 7.86%, $p < 0.01$) (fig. 1). Surprisingly, HbA_1c value at the time of diagnosis was higher in the group of patients secreting c-peptide, than non-secreting ones (11.35 vs 9.71 %, $p < 0.01$) (fig. 2).

Further analysis was performed to compare the subgroups according to the duration of the disease: less than 2 years, 2 to 5 years and longer than 5 yrs comprising of 48, 46 and 84 patients, respectively. C-peptide values in such selected subgroups were as follows: 1.47 ng/ml, 0.54 ng/ml and 0.17 ng/ml (fig. 3). Only in the group of patients suffering from diabetes mellitus for longer than 5 years did we find that: higher levels of c-peptide were found among patients with optimal glycemic control compared to patients with suboptimal glycemic control (0.44 vs 0.057 ng/ml, $p = 0.01$) (data not shown).

In order to find variables independently influencing actual c-peptide level we performed a regression analysis. We found that higher HbA_1c from the onset of the disease and older age at onset were determinants of the preserved c-peptide.

Finally, we compared both c-peptide measurement methods in order to determine if any of them is superior to the other. Interesting observation is that results obtained from both classic and ultrasensitive methods remain in great accordance and correlate very well with one another ($r=0.96$, $P<0.001$) (fig. 4). As it is shown, classic method is just as useful and reliable, in clinical setting, as ultrasensitive one.

Discussion

A few years ago it was believed that the autoimmune destruction of the pancreas in inevitable, but with new generation of ultrasensitive c-peptide measurement methods we have learned otherwise. It can be found even in patients suffering from diabetes mellitus for longer than 50 years [2]. Other studies revealed that residual pancreatic function plays a significant role in preventing serious complications like hypoglycemia, nephropathy and retinopathy [15,16]. Our observations confirm long-suspected correlation between residual pancreatic function measured as c-peptide levels and good metabolic control [7]. Well controlled glycemia enables some beta-cells to survive by lowering metabolic burden placed upon them [17]. What is more – remaining beta-cells can improve glycemic control by secreting insulin. Another possible explanation is a beneficial effect of c-peptide itself, postulated in numerous other publications [18,19]. Although c-peptide for long time was believed to be just a byproduct of insulin synthesis, now it is regarded as a biologically active compound, likely acting by surface G protein-coupled surface receptor. It was demonstrated that it can decrease renal glomerular hyperfiltration, albumin excretion and improve nerve function [18].

Considering metabolic control, we observed statistically lower HbA_1c values in patients with higher c-peptide levels. Surprisingly the link was seen only among patients with the duration of the disease longer than 5 years. According to the latest research studies, we may suspect it could be caused by partial regeneration of pancreatic beta-cells occurring in some patients with long-lasting disease [2].

It was noticed that patients currently secreting c-peptide, at the time of the diagnosis had higher HbA_1c than non-se-

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Table II. Comparison between patients with preserved c-peptide (group 1) vs non-preserved c-peptide (group 2) (clinically significant c-peptide level was set at 0,23 ng/ml according to DCCT data)
Tabela II. *Porównanie pomiędzy pacjentami z zachowanym wydzielaniem c-peptydu (grupa 1) vs z brakiem wydzielania (grupa 2) (klinicznie istotne wydzielanie c-peptydu ustalono na poziomie 0,23 ng/ml zgodnie z danymi DCCT)*

	Group 1/ Grupa 1	Group 2/ grupa 2	P value
Age (years)/ wiek (lata)	12.8 ± 3.4	12.8 ± 3.7	p = 0.94
Age at the time of diagnosis (years)/ wiek w czasie diagnozy choroby (lata)	10.1 ± 3.2	6.1 ± 3.4	p < 0.001
Duration of the disease (years)/ Czas trwania choroby (lata)	2.8 ± 2.4	6.7 ± 3.6	p < 0.001
Mean HbA1c from the last year (%)/ Średnia HbA_1c z ostatniego roku(%)	7.24 ± 0.87	7.86 ± 1.14	p < 0.001
HbA1c at the time of diagnosis (%)/ HbA_1c z okresu badania (%)	11.35 ± 2.32	9.71 ± 1.94	p < 0.001
Current BMI (kg/m^2)/ aktualne BMI	19.6 ± 3.2	20.3 ± 3.8	p = 0.27
Current/ aktualne SDS BMI	0.42 ± 0.84	0.70 ± 1.10	p = 0.11
BMI at the time of diagnosis (kg/m^2)/ BMI z czasu diagnozy choroby	17.0 ± 3.0	15.3 ± 2.7	p < 0.001
SDS BMI at the time of diagnosis/ SDS BMI z okresu diagnozy choroby	0 ± 0.98	-0.50 ± 1.10	p = 0.009
Remission duration (months)/ Czas remisji (miesiące)	10.7 ± 8.3	5.3 ± 6.3	p < 0.001
Total insulin dose (U/kg/24h) Całkowita dawka insuliny	0.71 ± 0.18	0.80 ± 0.20	p = 0.01
Basal insulin dose (U/24h)/ Podstawowa dawka insuliny	10.76 ± 5.42	13.91 ± 6.65	p = 0.003
Bolus insulin dose (U/24h)/ Dawka insuliny na bolusy	25.01 ± 11.80	26.30 ± 13.51	p = 0.55
Classic c-peptide level (mg/dl)/ c-peptyd metodą klasyczną	0.35 (0.16 – 0.60)	0.01 (0.01 – 0.02)	p < 0.001
Ultrasensitive c-peptide level (ng/ml)/ c-peptyd metodą ultrasensitive	1.5 (0.35 – 2.57)	0.0076 (0.0076 – 0.068)	p < 0.001

Data represented as mean ± standard deviation or median (interquartile range).
Dane przedstawione są jako średnia±odchylenie standardowe lub mediana (rozstęp kwartylowy).

creting ones. Although this fact is hard to explain in our study, we propose that the disease development in patients secreting c-peptide was more gradual, with no alarming symptoms for longer period of time. It could allow HbA_1c to reach higher levels without the individual being diagnosed. Although we did not assess the metabolic state of the patients at the time of the diagnosis (presence or severity of metabolic acidosis) we may speculate that, in older children, symptoms develop at slower pace [20]. Hyperglycaemia lasts longer without any alarming symptoms which results in higher HbA_1c level. This slow course of the disease could indicate that the destruction of the beta-cells can be caused by higher total mass of pancreas and more numerous beta-cells which could allow patients to preserve residual ability to secrete insulin for longer periods of time. Contrary, in younger children symptoms develop more rapidly. It could be caused by lower overall mass of pancreas, and what follows – fewer beta-cells, resulting in rapid destruction and loss of ability to secrete insulin [21]. Such rapid development of the disease is often accompanied by very high serum glucose levels and severe ketoacidosis, but does not allow enough time for HbA_1c to build-up.

In patients with clinically significant c-peptide levels, daily doses of insulin were lower. The relation was seen in both total and basal doses. It supports the theory that remaining secre-

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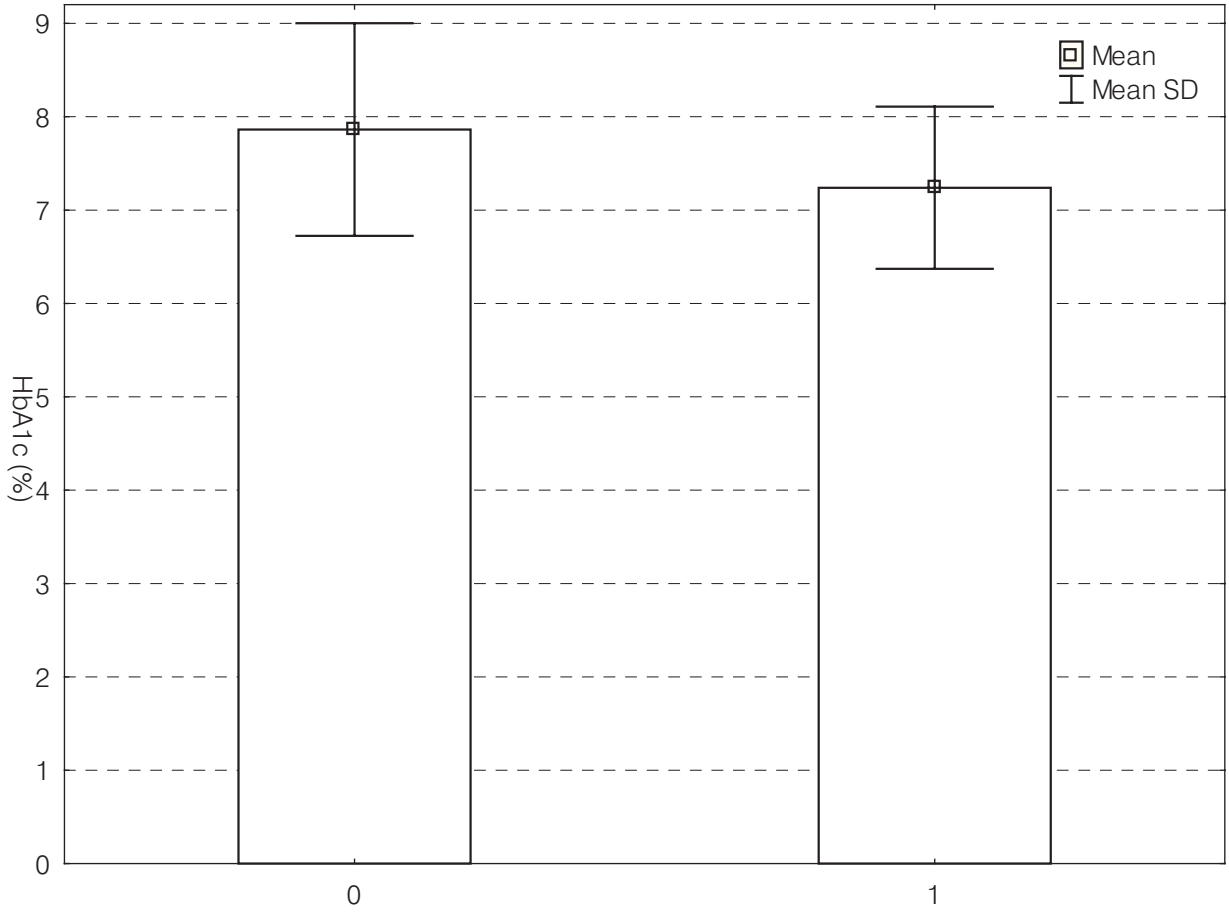

Fig. 1. Mean HbA_1c from the past year (%); 0 – patients with current c-peptide levels below clinical significance; 1 – patients with clinically significant current c-peptide levels
Ryc. 1. *Średnia wartość HbA_1c z ostatniego roku (%); 0 – pacjenci z klinicznie nieistotnym wydzielaniem c-peptydu, 1 – pacjenci z zachowanym klinicznie istotnym wydzielaniem c-peptydu*

tory function, even if only residual, remains clinically noticeable [20]. However, such relation was not seen in bolus doses. It could imply that damaged pancreas is able to provide some constant, basal secretion, but lacks the ability to provide clinically significant response to food intake, in spite of detectable increase in c-peptide after stimulation by standard mixed meal in laboratory settings [4].

Interestingly, patients currently secreting c-peptide, at the time of the diagnosis had higher SDS BMI than the other group. What is worth noting is that both groups had mean SDS BMI below 0. That could be caused by more significant weight loss due to an acute complication of diabetes in group 2 than 1. Now there is no difference between SDS BMI in both groups which confirms the thesis attributing it to acute complications. Another possible explanation is the previously proposed relation between total body mass and cumulative beta-cells mass. In this case, heavier patients would have more beta-cells to begin with, hence greater the functional pool of insulin-secreting cells. It could facilitate greater number of surviving cells and keeping higher levels of c-peptide [21].

A great number of patients, even the ones suffering from diabetes mellitus for long period of time, still have c-peptide levels high enough to detect them through classic method. It confirms observations contained in various other publications that the loss of beta-cells function in many cases is not complete and inevitable.Including c-peptide levels at the time of diagnosis and tracking its levels throughout the course of the disease could give us greater insight into the dynamics and pathogenesis of the disease. Comparing anti-pancreatic antibodies panel with c-peptide levels could draw interesting correlations between extent of autoimmune attack and residual pancreatic functionwhich implies that wider investigation on c-peptides role is clearly needed [2–5].

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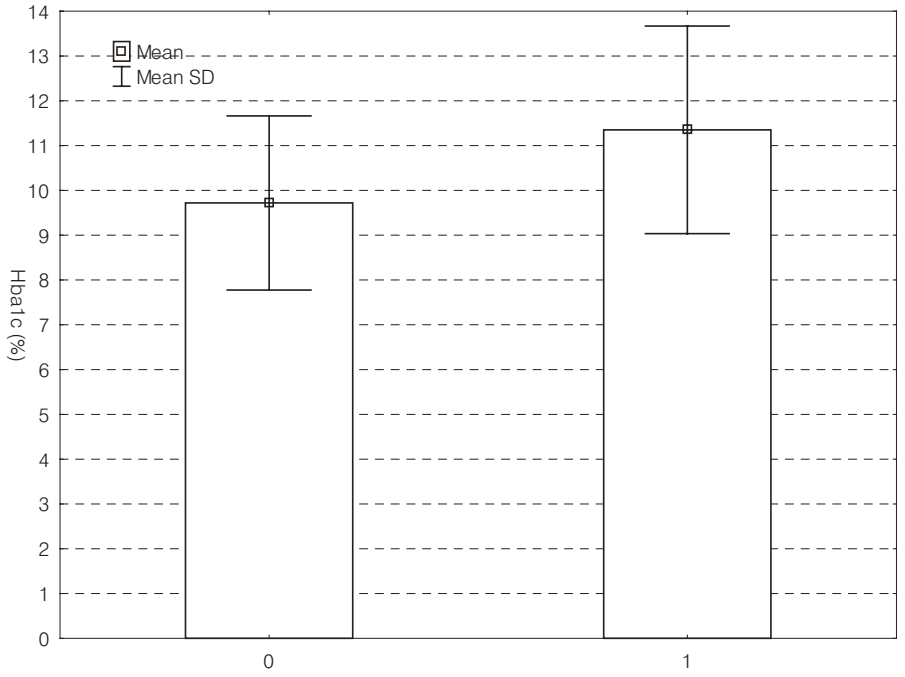

Fig. 2. HbA_1c at the time of the diagnosis (%); 0 – patients with current c-peptide levels below clinical significance; 1 – patients with clinically significant current c-peptide levels

Ryc. 2. *HbA_1c z czasu diagnozy cukrzycy (%); 0 – pacjenci z klinicznie nieistotnym wydzielaniem c-peptydu, 1 – pacjenci z zachowanym klinicznie istotnym wydzielaniem c-peptydu*

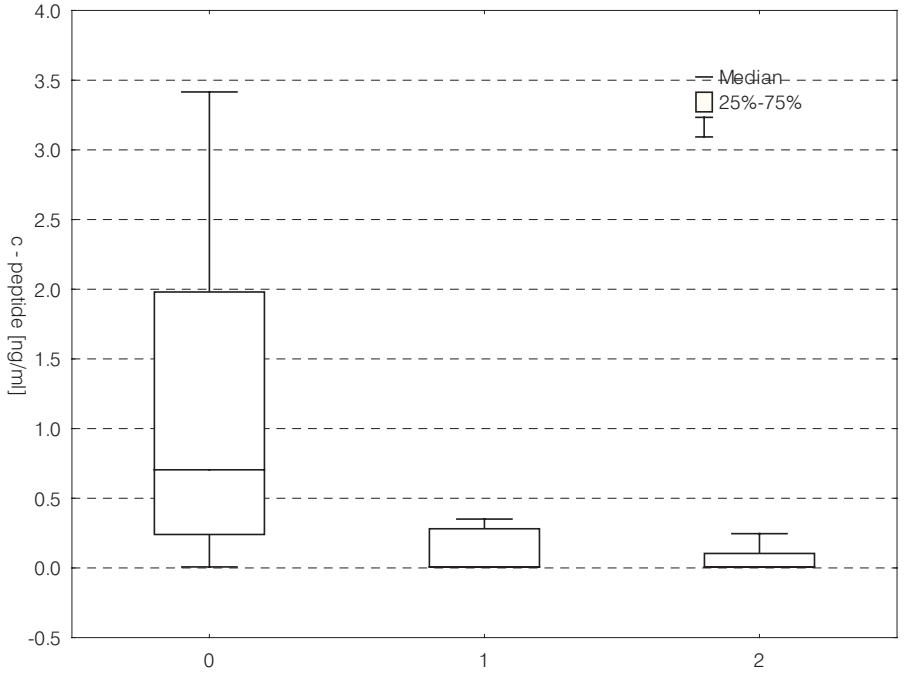

Fig. 3. Current c-peptide level (ng/ml); 0 – duration of the disease 2 or less; 1 – duration of the disease 2 to 5 years; 3 – duration of the disease more than 5 years

Ryc. 3. *Aktualne stężenie c-peptydu w zależności od czasu trwania cukrzycy; 0 – poniżej 2 lat, 1 – 2–5 lat, 2 – powyżej 5 lat*

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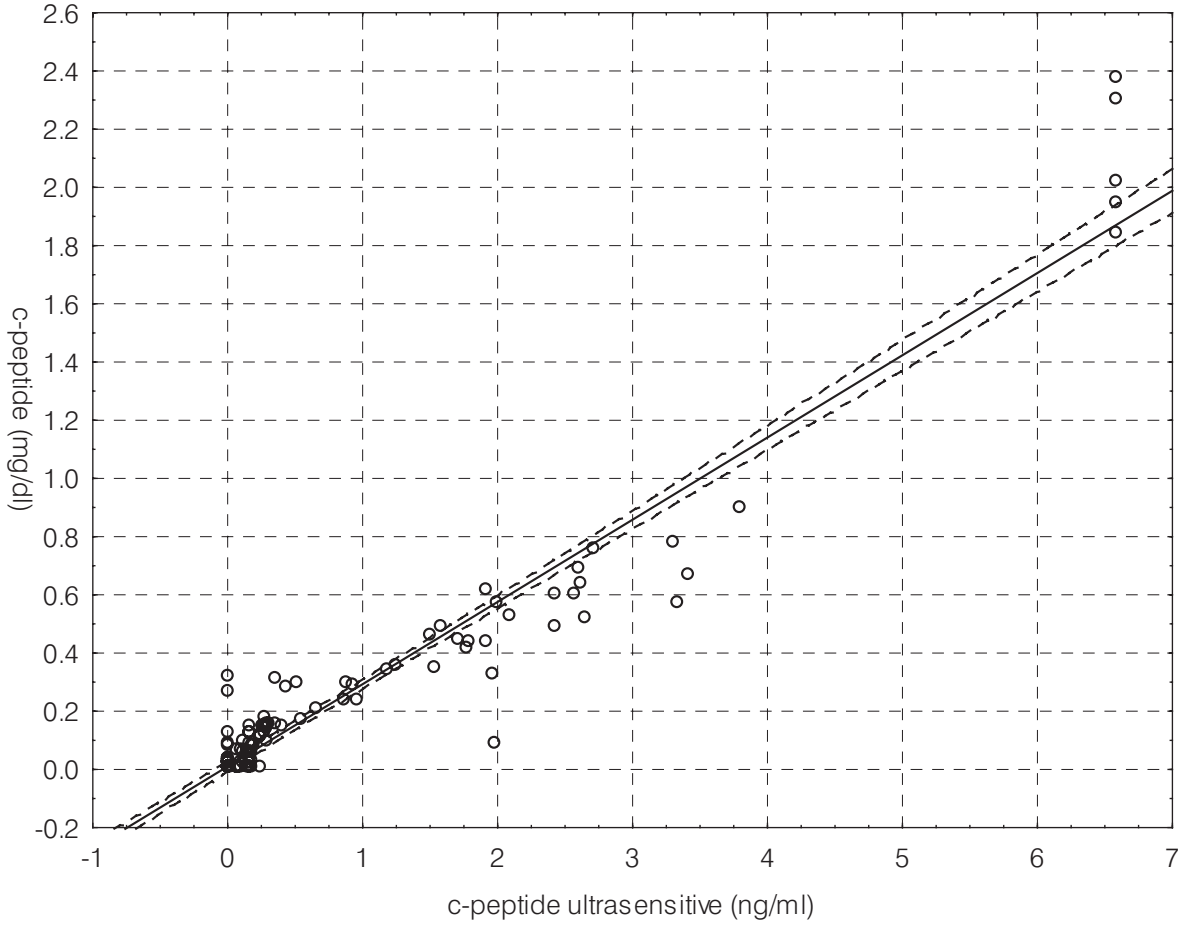

Fig. 4. Correlation analysis between "ultrasensitive c-peptide" and c-peptide level measured by routine laboratory method
Ryc. 4. *Analiza korelacji pomiędzy wynikami badania c-peptydu dwoma metodami oznaczania rutynową laboratoryjną oraz ultraczułą*

Both c-peptide measurement methods – ultrasensitive and classic – are viable for clinical usage. There is no obvious advantage in using ultrasensitive method as classic one is more readily available and just as reliable. Routine examination of c-peptide levels could help us determine the rate of beta-cells destruction and their remaining secretory function [22,23].

Our study has potential limitations. Greater diversity of ethnic background could reveal other factors, and better represent world's population. Larger cohort of patients would increase statistical power of the research. Not all children had c-peptide measured with ultrasensitive method. It was due to costs of the alternative possibility of measurement.

Conclusions

In young patients, even those suffering from diabetes mellitus for long period of time, c-peptide secretion can be preserved and correlates with better metabolic control, lower daily and basal insulin doses, but not with bolus doses. Higher c-peptide are more typical for shorter disease duration and older age of onset.There is no obvious advantage in using ultrasensitive method, as classic one is more readily available and just as reliable.

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