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# Leptin in acute myocardial infarction and period of convalescence in patients with type 2 diabetes mellitus

Przemysław Krasnodębski[1], Marianna I. Bąk[1], Grzegorz Opolski[2], Waldemar Karnafel[1]

[1]Department of Gastroenterology and Metabolic Diseases, Warsaw Medical University, Warsaw, Poland
[2]1st Department of Cardiology, Warsaw Medical University, Warsaw, Poland

## Abstract

**Background:** Leptin is a protein produced in adipose tissue and takes part in angiogenesis and atherogenesis. Leptin is associated with development of type 2 diabetes and cardiovascular disease.

**Aim:** To evaluate leptin concentrations in acute myocardial infarction and in the period of convalescence in patients with type 2 diabetes mellitus.

**Methods:** Coronary angiography was performed in 58 patients with acute myocardial infarction. The study group comprised 35 patients with type 2 diabetes mellitus (DM) (25 men, 10 women, mean age 63.8 ± 11.5 years) and 23 non-diabetic subjects (17 men, 6 women, mean age 58.6 ± 9.9 years) — the control group. All patients underwent medical examination and body mass indices (BMI) as well as waist/hip ratios (WHR) were calculated. Venous blood was collected after 24 hours of admission (second day), on day 5 and three weeks after admission.

**Results:** Leptin level was significantly associated with BMI (DM: $r = 0.46$, $p = 0.005$; control group: $r = 0.67$, $p < 0.01$), and hip circumference (DM: $r = 0.28$, $p = 0.09$; control group: $r = 0.41$, $p = 0.04$). Plasma leptin levels in women with type 2 diabetes were higher than in men (32.1 ± 11.7 μg/mL *vs* 12.7 ± 11.2 μg/mL, $p < 0.01$). Plasma leptin levels were significantly lower in non-diabetics compared to diabetic patients. Plasma leptin levels in diabetic patients were significantly higher in the acute phase of myocardial infarction than in the period of convalescence (18.3 ± 14.3 μg/mL, 16.1 ± 12.8 μg/mL, 14.8 ± ± 11.2 μg/mL, $p = 0.02$) but not in the control group (10.6 ± 8.2 μg/mL, 10.0 ± 7.3 μg/mL, 9.6 ± 7.0 μg/mL, NS).

**Conclusions:** Plasma leptin levels in diabetic patients were significantly higher in the acute myocardial infarction than in the period of convalescence. These findings suggests that leptin may play an important role in the metabolic changes taking place during the first days of myocardial infarction.

**Key words:** diabetes mellitus, myocardial infarction, leptin

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## INTRODUCTION

Cardiovascular diseases resulting from atherosclerosis are the most frequent complications of diabetes mellitus, and are responsible for 60–80% of deaths in diabetic patients. In-hospital mortality in patients with myocardial infarction (MI) and comorbid diabetes is 11.7% for ST-elevation myocardial infarction (STEMI) and 6.3% for non-ST-elevation MI (NSTEMI), and is much higher than in the non-diabetic population (6.4% for STEMI and 5.1% for NSTEMI) [1]. New aspects of interrelation between atherosclerosis and insulin resistance are being searched for continuously. Among these, the role of adipose tissue and its products — adipokines, is increasingly emphasised, due to their relevance for numerous metabolic processes. Despite growing knowledge on the role of adipo-

**Address for correspondence:**
dr n. med. Przemysław Krasnodębski, Department of Gastroenterology and Metabolic Diseases, Warsaw Medical University, ul. Banacha 1a, 02–097 Warsaw, Poland, tel: +48 22 599 28 38, fax: +48 22 599 18 38, e-mail: pkrasnod@wp.pl
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cytokines, their direct effects on the pathogenesis of acute coronary syndromes are still difficult to define.

Leptin is one of the adipocytokines produced by white adipose tissue, although its synthesis was also detected in the hypophysis, placenta, breasts, skeletal muscles and gastric mucosa [2]. Leptin is a protein of molecular weight of 16 kD, consisting of 167 aminoacids, and its levels are dependent on the amount of adipose tissue and size of adipocytes. Leptin secretion has its diurnal variation with circa 32 pulses, peaking during nighttime, and is greater in women [2]. Leptin synthesis is stimulated by insulin, estrogens, corticosteroids and TNF-$\alpha$ [2, 3]. Conversely, the growth hormone, testosterone and long fasting reduce leptin secretion. In non-diabetic patients a significant correlation was found between leptin concentration and insulin resistance as measured by HOMA-IR index four months after MI [4]. Leptin effects on haematopoesis and angiogenesis through stimulation of proliferation and migration of endothelial cells have also been demonstrated [5] thus promoting plaque growth. Among US inhabitants, higher leptin concentrations were found in patients with a history of MI or stroke [6].

The aim of the study was to analyse the dynamic leptin concentration changes in acute phase of MI and during the period of convalescence in type 2 diabetic patients.

## METHODS

### *Study group*

Fifty-eight patients admitted to hospital for acute MI at the end of 2005 and at the beginning of 2006 were included in the study. Thirty-five patients with at least 6-month history of diabetes formed the study group. The control group consisted of 23 patients in whom no glucose tolerance disorders were diagnosed. In these patients, impairment of glucose tolerance was additionally excluded on the basis of glucose tolerance test carried out on day 21 from symptom onset. Only patients with ECG and biochemical criteria of MI and time from symptom onset < 12 hours were included in the study. The study protocol was approved by the local bioethical committee. All patients gave their informed written consent. In all patients coronary angiography was carried out and in patients with significant coronary stenosis — primary coronary angioplasty was performed. Table 1 presents comparison of demographic and clinical characteristics of the studied groups.

### *Study design and laboratory workup*

Plasma leptin concentrations were assessed by radioimmunoenzymatic assay (RIA) between 24 and 48 hours of MI, after the night break and not earlier than 6 hours after coronary angiography. Then plasma leptin levels were assessed on day 5 and day 21. Anthropometric measurements (body weight, height, waist and hip circumference) were also carried out, and waist-to-hip ratio and body mass index (BMI) were calculated.

### *Statistical analysis*

Results were displayed as means ± standard deviation or as absolute numbers and percentages. Statistical analysis was carried out with Polish version of Statistica 7.1.340.0 statistical package (StatSoft Inc), licensed for academic use at Warsaw Medical University. Leptin concentration differences between the study groups were assessed by Mann-Whitney U-test, and Spearman's test was used for correlations. To assess differences between leptin concentrations measured at different time points, Friedman's rank test was used. Statistical significance threshold was set at 5%.

## RESULTS

The studied groups did not differ significantly in terms of age, sex and lipid profile (Table 1), whereas smaller number of diabetic patients were smokers. In all the three measurements (i.e. on day 2, day 5 and day 21), leptin concentrations in diabetics were higher than in the control group (Table 2). Moreover, in the diabetic patients, a significant decrease of leptin concentrations throughout the study was observed ($p = 0.02$) (Fig. 1). This was not observed in non-diabetic patients ($p = 0.59$) (Fig. 1). In all measurements, leptin concentrations were higher in women than in men, both in diabetic (Fig. 2) and non-diabetic (Fig. 3) patients. In both study groups, leptin concentrations correlated positively with BMI (Figs. 4, 5) as well as with glucose levels and hip circumference (Table 3). Leptin concentrations in patients with NSTEMI were not significantly different from concentrations observed in STEMI patients. Correlations of leptin concentrations with the remaining anthropometric and biochemical parameters are presented in Table 3.

## DISCUSSION

In the present study, significantly higher leptin concentrations during the acute phase of MI in comparison with the convalescence period were observed only in diabetic patients. To date, it has been suggested that increased sympathetic activation can directly increase hyperleptinaemia [7]. This mechanism can be responsible for significantly higher leptin concentrations in the acute phase of MI in diabetic patients and for subsequent gradual decrease of the hormone concentration at the later stages. It should also be underlined that leptin synthesis is stimulated, among other factors, by glycocorticosteroids and insulin [3], and that in the course of MI, especially in type 2 diabetic patients, tissue insulin sensitivity decreases, resulting in hyperinsulinaemia.

Elevated leptin concentrations that are observed during the first days of MI can be particularly harmful in patients with type 2 diabetes, as leptin stimulates gluconeogenesis and fatty acid synthesis in the liver, inhibits insulin secretion in pancreatic B-cells and potentially accelerates insulin receptor degradation [3]. Elevated leptin concentrations in diabetic patients can therefore represent another link further incre-

**Table 1.** Comparison of demographic and clinical characteristics of the studied groups

| Clinical characteristic | Diabetics (n = 35) | Non-diabetics (n = 23) | P |
|---|---|---|---|
| Sex | | | 0.83 |
| Men | 25 (71.4%) | 17 (73.9%) | |
| Women | 10 (28.6%) | 6 (26.1%) | |
| Age [years] | 63.8 ± 11.5 | 58.6 ± 9.9 | 0.08 |
| Body mass index [kg/m$^2$] | 29.4 ± 3.9 | 27.9 ± 3.2 | 0.15 |
| Waist to hip ratio | | | |
| Women | 0.93 ± 0.03 | 0.89 ± 0.056 | 0.13 |
| Men | 1.01 ± 0.03 | 0.96 ± 0.04 | < 0.01 |
| Waist circumference [cm] | | | |
| Women | 92 ± 9.2 | 85 ± 5.9 | 0.1 |
| Men | 99.7 ± 10.7 | 94.6 ± 10.5 | 0.13 |
| Hip circumference [cm] | | | |
| Women | 98.9 ± 8.0 | 94.8 ± 5.7 | 0.3 |
| Men | 98.2 ± 9.2 | 98.4 ± 9.3 | 0.9 |
| Smoking | 8 (36%) | 14 (60%) | < 0.01 |
| Hypertension | 28 (80%) | 12 (52.5%) | 0.02 |
| Ejection fraction | 48.7 ± 9.5 | 52.7 ± 8.4 | 0.09 |
| ST-elevation myocardial infarction | 22 (62.8%) | 18 (78%) | 0.21 |
| Cholesterol [mg/dL] | 176 ± 47 | 197 ± 33 | 0.06 |
| HDL cholesterol [mg/dL] | 40.5 ± 8.2 | 45.6 ± 11.3 | 0.05 |
| LDL cholesterol [mg/dL] | 115.2 ± 47.5 | 132.8 ± 40.3 | 0.14 |
| Triglycerides [mg/dL] | 173 ± 90 | 152 ± 87 | 0.1 |
| $HbA_{1c}$ concentration [%] | 8,0 ± 1,5 | 5.8 ± 0.4 | < 0.01 |
| Glucose concentration | | | |
| Day 2 | 154.7 ± 40.2 | 115.1 ± 17.8 | < 0.01 |
| Day 5 | 152.7 ± 48.1 | 112.7 ± 19.1 | < 0.01 |
| Day 21 | 142.7 ± 38.5 | 108.8 ± 13 | < 0.01 |

**Table 2.** Leptin concentrations [$\mu$/mL] in the studied groups

| | Diabetics | Non-diabetics | P |
|---|---|---|---|
| Day 2 | 18.3 ± 14.33 | 10.66 ± 8.28 | 0.03 |
| Day 5 | 16.17 ± 12.88 | 10.08 ± 7.35 | 0.05 |
| Day 21 | 14.84 ± 11.22 | 9.66 ± 7.02 | 0.07 |

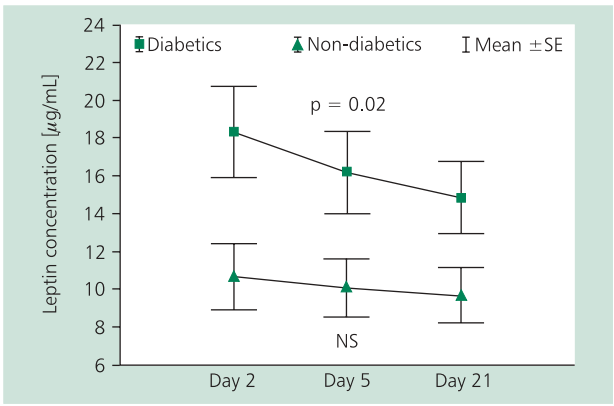


**Figure 1.** Leptin concentration in the studied groups at various time-points

asing peri-infarction hyperglycaemia, which adversely influences prognosis, in terms of higher rates of early and late mortality [8]. Our study also confirms the link between leptin and hyperglycaemia in the acute phase of MI, as leptin concentrations correlated directly with glucose levels. Markedly higher leptin concentrations can play an important role in the course of MI in diabetic patients also by influencing endogenous fibrinolysis, endothelial function, platelet aggregation, insulin resistance and prothrombotic mechanisms, as well as by sympathetic activation. The extent of metabolic and pathophysiological disturbances occurring in diabetic patients in the course of MI is underestimated and too often

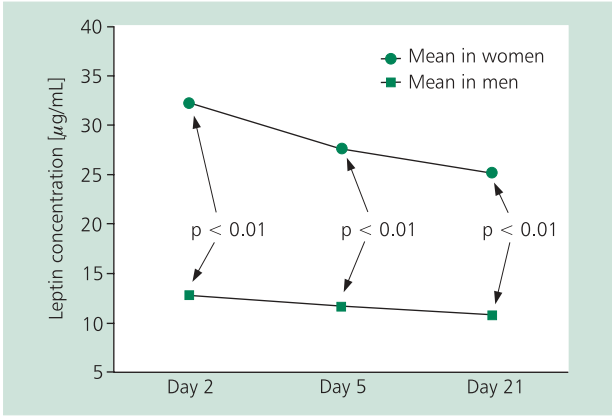


**Figure 2.** Comparison of leptin concentration in diabetic males and females at different time-points

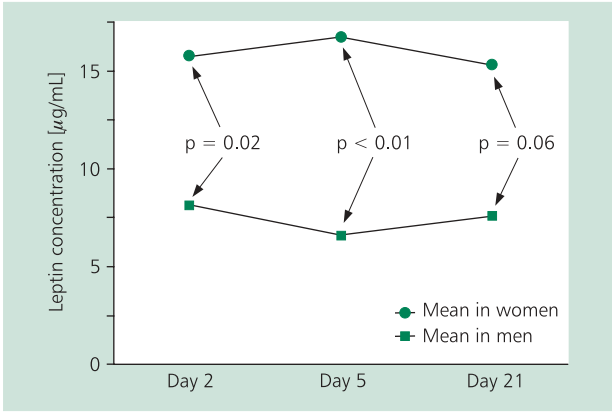


**Figure 3.** Comparison of leptin conentration in non-diabetic males and females at different time-points

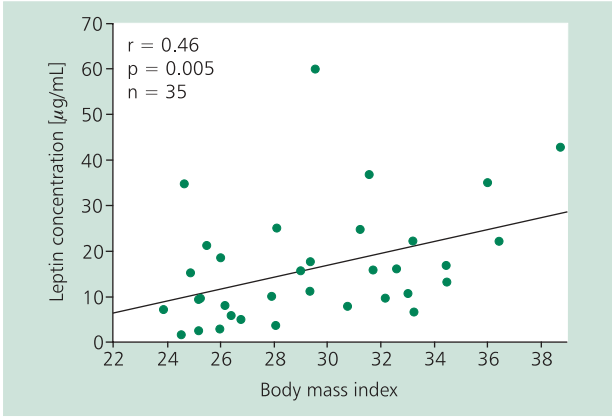


**Figure 4.** Correlation between BMI and leptin concetration in diabetics

neglected. Concurrent stress is an additional factor increasing leptin secretion in the course of MI. However, according to some authors, the increase of leptin concentrations in response to stress can be a reaction facilitating adaptation to these circumstances [9].

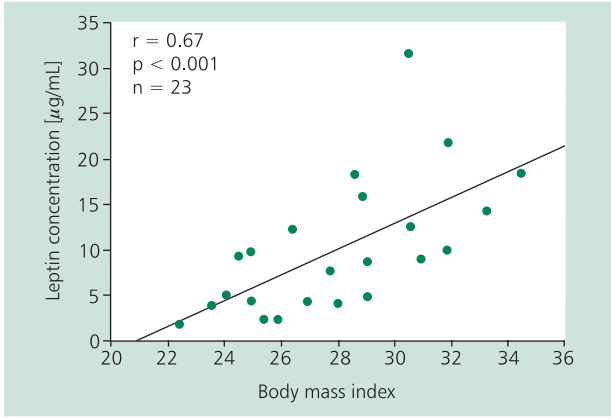


**Figure 5.** Correlation between BMI and leptin concentration in non-diabetics

**Table 3.** Correlation of leptin concentrations with anthropometric and biochemical parameters

| | Diabetics (n = 35) | Non-diabetics (n = 23) |
|---|---|---|
| Glucose | r = 0.5<br>p < 0.01 | r = 0.53<br>p < 0.01 |
| Cholesterol | r = 0.29<br>p = 0.08 | r = 0.21<br>p = 0.3 |
| Triglycerides | r = 0.23<br>p = 0.1 | r = 0.35<br>p = 0.09 |
| HDL-cholesterol | r = –0.26<br>p= 0.1 | r = –0.1<br>p = 0.9 |
| LDL-cholesterol | r = 0.23<br>p = 0.1 | r = 0.1<br>p = 0.4 |
| Body mass index | r = 0.46<br>p = 0.005 | r = 0.67<br>p < 0.01 |
| Waist circumference | r = 0.03<br>p = 0.8 | r = 0.3<br>p = 0.14 |
| Hip circumference | r = 0.28<br>p = 0.09 | r = 0.41<br>p = 0.04 |
| Waist to hip ratio | r = 0.03<br>p = 0.07 | r = 0.05<br>p = 0.8 |

Leptin concentrations at every time point throughout the study were significantly different in diabetics in comparison with controls. This held true also in the convalescence period, what can be of importance in terms of evaluation of further course of diabetes as well as possible ischaemic potential in diabetics with history of MI. Higher leptin levels found in diabetic patients further increase the proliferation and migration of the endothelial cells [5], thus contributing to atherosclerotic plaque growth. It can also be taken into consideration that leptin can enhance oxidative stress in the endothelium, further promoting atherogenesis [10]. However, to date, the role of leptin in the pathogenesis of MI has not been

unequivocally confirmed. Also, leptin as a prognostic factor in diabetic patients with MI merits further study.

In the studies published to date, higher leptin concentrations were observed in patients with MI in comparison with patients with stable angina or in patients without history of coronary artery disease (CAD) [11, 12]. Meisel et al. [9] reported decreasing leptin concentrations at day 3 and day 4 of MI, but their study did not concentrate on diabetic patients and they did not analyse the convalescence period. It seems that analysis of leptin concentrations over several weeks after MI could have not only cognitive, but also prognostic value concerning further course of CAD as well as of diabetes itself. Te role of increased leptin concentration in the pathophysiology of MI was demonstrated in the study by Taneli et al. [11]. However, dynamic leptin concentration changes were not investigated, and MI group consisted of STEMI patients only.

In our study, leptin concentrations in diabetic patients were the highest on day 2 post-infarction and they gradually decreased in subsequent measurements. Mechanism, and above all, the consequences of these disturbances are not entirely clear. Undoubtedly, the endogenous lipid hydrolysis, which is augmented during the course of infarction, plays a role. Concurrently, free fatty acid usage as the main source of energy is restricted, what enables their accumulation in the ischaemic cardiomyocyte and makes them the primary substrate for energy production. Thus, glucose oxidation is further decreased under conditions of peri-infarction hyperglycaemia. Moreover, elevated leptin concentrations accompanying the increased sympathetic activation could correlate with levels of glucagon, a hormone enhancing insulin resistance by antagonising insulin activity.

Leptin can promote vasoconstriction due to stimulation of sympathetic activity, but, on the other hand, it promotes vasodilatation by enhancing nitric oxide production. Also, increased expression of leptin gene was noted in rat models with myocardial ischemia [13]. Another study showed that leptin signalling reduces the severity of cardiac dysfunction and remodelling after chronic ischaemic injury [14].

Proinflammatory cytokine interleukin-6 (IL-6) plays an important role in CAD pathogenesis, and its high levels were shown to adversely influence prognosis in heart failure. It is conceivable, that IL-6 can indirectly promote myocardial dysfunction in MI. It was demonstrated that on the second day of infarction leptin concentration increased and that it inversely correlated with IL-6 levels. Hence, a hypothesis was put forward, that leptin could play a role in the pathophysiology of the heart, not only by pressure regulation via sympathetic activation [15].

In our study leptin concentrations directly correlated with the extent of obesity, thus confirming the previously published results. It should be added , however, that under conditions of hyperleptinaemia a decrease in leptin receptor number may occur and tissue resistance to the hormone can develop. It is believed to represent one of the mechanisms promoting the development of obesity.

## CONCLUSIONS

In the acute phase of myocardial infarction in diabetic patients, significantly higher leptin concentrations are observed in comparison with convalescence period. This can be related to significant detrimental metabolic changes taking place during the first days of infarction in these patients.

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# Analiza stężenia leptyny u chorych na cukrzycę typu 2 w ostrej fazie zawału serca i w okresie rekonwalescencji

Przemysław Krasnodębski[1], Marianna I. Bąk[1], Grzegorz Opolski[2], Waldemar Karnafel[1]

[1]Katedra i Klinika Gastroenterologii i Chorób Przemiany Materii, Warszawski Uniwersytet Medyczny, Warszawa
[2]I Katedra i Klinika Kardiologii, Warszawski Uniwersytet Medyczny, Warszawa

## Streszczenie

**Wstęp:** Produkowana przez tkankę tłuszczową leptyna może uczestniczyć w angiogenezie i aterogenezie oraz w modulacji odpowiedzi zapalnej czy aktywacji mechanizmów prozakrzepowych. Podkreśla się również rolę podwyższonych stężeń leptyny w rozwoju cukrzycy typu 2 i progresji choroby wieńcowej.

**Cel:** Celem pracy była analiza dynamiki zmian stężenia leptyny u chorych na cukrzycę typu 2 w ostrej fazie zawału serca i w okresie rekonwalescencji.

**Metody:** Do badania zakwalifikowano 58 pacjentów z ostrym zespołem wieńcowym, w tym 35 z cukrzycą typu 2 (10 kobiet, 25 mężczyzn; wiek 63,8 ± 11,5 roku) i 23 osób bez cukrzycy (17 mężczyzn, 6 kobiet; wiek 58,6 ± 9,9 roku), które stanowiły grupę kontrolną. Stężenia leptyny oznaczono metodą radioimmunoenzymatyczną (RIA) w próbkach pobranych na czczo w 2., 5. i 21. dobie zawału. Wykonano również pomiary antropometryczne, wyliczono wskaźnik masy ciała (BMI) i wskaźnik talia/biodra (WHR). Podczas analizy statystycznej wykorzystano test U Manna-Whitneya, test $\chi^2$ oraz test rang Friedmana.

**Wyniki:** W obu grupach zaobserwowano istotną dodatnią korelację między stężeniem leptyny a BMI (u chorych na cukrzycę: $r = 0,46$; $p = 0,005$; w grupie kontrolnej: $r = 0,67$; $p < 0,01$) oraz obwodem bioder (u chorych na cukrzycę: $r = 0,28$; $p = 0,09$; w grupie kontrolnej: $r = 0,41$; $p = 0,04$). Stężenie leptyny u kobiet z cukrzycą typu 2 było wyższe niż u mężczyzn (32,1 ± 11,7 μg/ml *v.* 12,7 ± 11,2 μg/ml; $p < 0,01$). We wszystkich okresach zawału stężenia leptyny u chorych na cukrzycę typu 2 były wyższe niż w grupie kontrolnej. Ponadto u chorych na cukrzycę wykazano istotne obniżanie się stężeń leptyny w kolejnych etapach obserwacji (18,3 ± 14,3 μg/ml *v.* 16,1 ± 12,8 μg/ml *v.* 14,84 ± 11,2 μg/ml; $p = 0,02$). Zależności tej nie stwierdzono u osób bez cukrzycy (10,6 ± 8,2 μg/ml *v.* 10,0 ± 7,3 μg/ml *v.* 9,6 ± 7,0 μg/ml; $p = 0,59$).

**Wnioski:** W ostrej fazie zawału u chorych na cukrzycę obserwuje się znamiennie wyższe stężenia leptyny niż w okresie rekonwalescencji, co może świadczyć o istotnych niekorzystnych zmianach metabolicznych zachodzących w pierwszych dniach zawału u tych pacjentów.

**Słowa kluczowe:** cukrzyca, zawał serca, leptyna

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**Adres do korespondencji:**
dr n. med. Przemysław Krasnodębski, Katedra i Klinika Gastroenterologii i Chorób Przemiany Materii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02–097 Warszawa, tel: +48 22 599 28 38, faks: +48 22 599 18 38, e-mail: pkrasnod@wp.pl
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