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Seasonal effect of vitamin D deficiency in patients with acute myocardial infarction

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Abstract

Background: Vitamin D is a major regulator of mineral bone metabolism. The lower vitamin D levels in patients with acute myocardial infarction (AMI) and the seasonal variation of vitamin D levels is proposed.

Aim: The aim of the study was evaluation of the seasonal relationship of 25(OH)D levels in patients with AMI and analysis of confounding factors (gender or diabetes mellitus) affecting the levels of vitamin D in AMI patients.

Methods: Fifty nine consecutive patients in mean age 58 ± 9.4 years were admitted to the Department of Invasive Cardiology. Subjects had diagnosed uncomplicated myocardial infarction. Blood samples for analysis were collected on patient admission to the cardiac unit, after heparin treatment. Samples for routine laboratory tests were immediately processed. For 25-(OH)D, the 25-hydroxycholecalciferol test which measures total vitamin D levels in serum (DRG Instruments GmbH, Marburg, Germany) was applied.

Results: Median serum 25(OH)D concentration in AMI patients was below the recommended optimal values 7.1 (2.3-13.3) ng/mL. Fifty three patients (89.8%) had vitamin D deficiency

(VDD) below 20 ng/mL, and 6 patients (10.2%) had suboptimal 25(OH)D levels (between 20 and 30 ng/mL) and no one had the recommended reference range. The seasonal effect of 25(OH)D variations among AMI patients was observed with the lowest levels in the beginning of the year (January-March) and the highest levels in the end of the year (September-December) (p=0.007). Patients with normoglycemia had significantly higher (9.2 (2.3-16.8) ng/mL) vitamin D levels compared to patients with impaired glucose tolerance (2.3 (2.3-3.9) ng/mL) or diabetes mellitus (8.5 (2.5-13.3) ng/mL)) (p=0.01).
Conclusions: High prevalence of VDD in AMI patients has been confirmed. Supplementation of vitamin D in AMI patients with hyperglycemia can bring greater benefits.
Key words: vitamin D, cardiovascular risk, myocardial infarction, clinical biochemistry

Sezonowe zmiany w niedoborach witaminy D u chorych z zawałem serca

Streszczenie

Wstęp: Witamina D jest głównym regulatorem metabolizmu kostnego. W ostatnich latach obserwuje się ogromny wzrost zainteresowania witaminą D. Ze względu na jej receptorowe działanie, coraz częściej traktowana jest ona nie tylko jako witamina, ale również jako hormon sterydowy. Klasyczna aktywność witaminy D nierozerwalnie związana jest z gospodarką mineralną: utrzymuje homeostazę wapniowo – fosforanową oraz kontroluje metabolizm kostno – szkieletowy. Aktywną hormonalnie formą witaminy D jest kalcytriol lub 1α,25-dihydroksykalcyferol (1α,25$(OH)_2D_3$). W przeciwieństwie do 25-hydroksywitaminy D (25(OH)D), która jest prohormonem i głównym krążącym metabolitem witaminy D, poziom (1α,25-$(OH)_2D_3$) jest około 1000-krotnie niższy niż 25(OH)D. Pomimo tego, że 1α,25$(OH)_2D_3$ ukazuje biologicznie aktywną postać witaminy D, jest powszechnie akceptowane, że to poziom 25(OH)D jest wskaźnikiem stanu witaminy D u chorych, szczególnie u tych z niedoborami witaminy D. Postuluje się, że u chorych z zawałem serca występują niskie poziomy witaminy D, które mogą ulegać sezonowej zmienności.
Cel: Głównym celem niniejszego badania była ocena sezonowej zmiany poziomu witaminy D (25(OH)D) u chorych z ostrym zawałem serca (AMI- acute miocardial infarction). Drugim celem było zbadanie, czy czynniki takie jak płeć lub cukrzyca mają związek z poziomem 25(OH)D u tych chorych.
Metody: Do badania włączono 59 chorych (śr. wieku 58 ± 9.4 lat) przyjętych na oddział kardiologii interwencyjnej. U chorych stwierdzono ostry zawał serca, bez powikłań. Próbki krwi pobrano od chorych po podaniu heparyny ~~i~~ wykonująca~~no~~ jednocześnie rutynowe

oznaczenia. Pomiar stężenia 25(OH)D - witaminy D wykonano z zastosowaniem metody immunoenzymatycznej (analizator HYBRID XL, DRG, Marburg, Niemcy).
Wyniki: Otrzymane wyniki interpretowano w odniesieniu do wytycznych stworzonych dla populacji Europy Środkowej. Stężenie 25(OH)D poniżej 20 ng/mL traktowane jest jako deficyt, między 20 a 30 ng/mL charakteryzuje suboptymalne zaopatrzenie organizmu w witaminę, natomiast wartości prawidłowe, docelowe dla suplementacji wynoszą między 30 a 50 ng/mL. Wartość mediany dla 25(OH)D mieściła się poniżej zalecanej normy: 7,1 (2,3-13,3) ng/mL. Niedobór witaminy D poniżej 20 ng/mL stwierdzono u 53 chorych (89.8%) chorych, 6 chorych (10.2%) miało niskie stężenia (między 20 a 30 ng/mL), u żadnego chorego nie stwierdzono prawidłowego poziomu witaminy D. Zaobserwowano również sezonowe zmiany w stężeniach 25(OH)D: najniższe na początku roku (styczeń-marzec), a najwyższe między wrześniem a grudniem (p=0.007). Chorzy z wyrównaną glikemią mieli znacząco wyższe stężenia witaminy D (9.2 (2.3-16.8) ng/mL) niż chorzy z nieprawidłową tolerancją glukozy (2.3 (2.3-3.9) ng/mL) lub cukrzycą (8.5 (2.5-13.3) ng/mL)) (p=0.01).
Wnioski: Potwierdzono znaczące niedobory witaminy D u chorych z zawałem. Potwierdzony wysoki odsetek chorych z niedoborem witaminy D w grupie AMI powinien być traktowany jako dodatkowy czynnik ryzyka oraz czynnik zakłócający dla chorób układu krążenia. U osób po przebytym AMI należy wziąć pod uwagę monitorowanie stężenia witaminy D (25(OH)D) ze względu na jej niedobór i konieczną suplementację, oraz celem uniknięcia przedawkowania witaminy D. Chorzy z hiperglikemią mogą również osiągnąć większą korzyć z suplementacji witaminy D w porównaniu do chorych z wyrównanym poziomem glukozy.
Słowa kluczowe: witamina D, diagnostyka laboratoryjna, czynniki ryzyka, zawał

INTRODUCTION

Nowadays, a large increase in interest in vitamin D as a potential dietary factor contributing in cardiovascular diseases has been observed [1,2]. It has been recently reported that lower vitamin D levels may be associated with poor collateral vasculature development in patients with stable CAD [3]. The other cross-sectional analyses showed the associations between lower vitamin D levels and the risk of cardiovascular diseases or poor prognosis for patients with major adverse events (MACE) [3-6]. Moreover, the association between vitamin D deficiency (VDD) and endothelial dysfunction is well established [7] .

In the organism, vitamin D is a major regulator of bone metabolism. However, recent data indicate their pleiotropic action in various biological processes, thus vitamin D is considered to be a steroid hormone involved in the intestinal absorption of calcium and the regulation of calcium homeostasis. The hormonally active form of vitamin D is calcitriol or 1α,25 dihydroxcalciferol D (1α,25-$(OH)_2D_3$). In contrast to 25-hydroxyvitamin D (25(OH) D_3) which is a prohormone and the major circulating metabolite of vitamin D, the levels of 1α,25$(OH)_2D_3$ are about 1000-fold lower that of 25$(OH)D_3$. Although, 1α,25$(OH)_2D_3$ portrays the biological active form of vitamin D, it is widely accepted that 25(OH)D is the robust indicator of vitamin D status in individuals, especially in hypovitaminosis or VDD [6].

In humans, cutaneous synthesis of vitamin D is responsible for > 90% of 25(OH)D levels in the serum and some seasonal variations in circulating vitamin D levels have been observed, especially for Northern and Central Europe populations [8,9]. However, it is still not well recognized if is any relationship between seasonal variation of 25(OH)D levels and incidence of AMI [4]. These associations might probably explain the observed relationship between a seasonal periodicity of cardiovascular mortality with a winter peak and summer nadir [11,12].

The aim of the present study was to evaluate the seasonal relationship of 25(OH)D levels in patients admitted to an interventional cardiology unit because of AMI. The second aim was to investigate if there are any confounding factors (gender or diabetes mellitus) affecting the levels of vitamin D in AMI patients.

METHODS

Fifty nine consecutive patients (n=46 of men) in mean age 58 ± 9.4 years (range from 40 to 79) were admitted to the Department of Invasive Cardiology, The Edward Szczeklik Hospital in Tarnow (Poland) between July 2010 and March 2013. Patients had diagnosed uncomplicated myocardial infarction according to the ESC/AHA redefined guidelines [13,14]. According to the same criteria patients were classified as STEMI (n=23) and NSTEMI (n=36). All patients underwent urgent coronary angiography and subsequent coronary intervention according to guidelines. In order to analyze the seasonal variation of 25(OH)D levels patients were distributed to 4 groups according to the time of admission: (1) January-March, (2) April-June, (3) July-September and (4) October-December.

Inclusion criteria were as follows: presence of infarct-related lesion in coronary artery identified during routine coronary angiography [15]. Additional inclusion criterion was the information about restraining of vitamin D supplementation. Estimated glomerular filtration

rate (GFR) was below 60 mL/min/1.73m^2. Exclusion criteria were as follows: any clinical signs of heart failure (in Killip classes II, III and IV) observed before catheterization, prior fibrinolysis, mechanical or electrical complications of ACS, left bundle branch block on ECG, anticoagulation, known malignant disease, active or chronic infection or other inflammatory disease. All subjects signed their informed consent with accordance with the requirements of the institutional local Ethics Committee.

The distribution of classic risk factors (diabetes, arterial hypertension and smoking status) were recorded (Table 1). Definitions of hypertension and diabetes were adopted from the scientific statements of the European Society of Cardiology (http://www.escardio.org). Impaired glucose tolerance (IGT) was defined as two-hour glucose levels rise from 7.8 to 11.0 mmoL in the 75-g oral glucose tolerance test. Diabetes mellitus (DM) was classified according to the IDF guidelines (2012) [16].

Blood sampling

Blood samples for analysis were collected on patient admission to the cardiac unit, after heparin treatment. Samples for routine laboratory tests were immediately processed. Serum for 25-(OH)D analysis was allowed to coagulate for 30 min, centrifuged (2 000 G for 10 min) and frozen at –80°C until further assessment.

Laboratory tests

The routine blood tests included serum glucose, creatinine, hs-CRP, fibrinogen levels and lipid profile assessment. Cardiac troponin cTnT levels were analyzed by means of the high sensitivity test (Roche Diagnostics, Basel, Switzerland) during admission. The cut-off for AMI was set on the level above 14 ng/mL. For 25(OH)D we used the 25-hydroxycholecalciferol test witch measures total vitamin D levels in serum (Cat. No. HYE-5334, DRG Instruments GmbH, Marburg, Germany). The method is applied as competitive solid phase enzyme – linked immunosorbent assay (ELISA) on the HYBRID XL analyzer (DRG Instruments GmbH, Marburg, Germany). The assay is based on competition of the endogenous form of 25(OH)D with the 25(OH)D-biotin conjugate for binding to the well-coated Vitamin D Binding Protein (VDBP). After incubation, unbound conjugate is wash off and bound 25(OH)D-biotin conjugate is detected by streptavidin-peroxidase conjugate. Concentration of 25(OH)D in a patient sample is inversely proportional to the amount of detected peroxidase. The result is the effect of additive concentrations of 25(OH)D_3 and 25(OH)D_2. This assay detected vitamin D_2 with specificity 74.7% and vitamin D_3 with 100%.

The dynamic range of the assay is defined such as limit of detection and maximal value on the master curve. The range of assay is between 2.3-130 ng/mL. The sensitivity of the method is identical with the beginning of the dynamic range. The total assay precision is 14.6%. The reference range for Central Europe population was recommended on optimal (target) serum 25(OH)D concentrations ranging from 30 to 50 ng/mL (75–125 nmol/L) [9].

Statistical analysis

It was established whether the continuous data followed the normal distribution by the Kolmogorov-Smirnov test. Continuous variables are presented as the mean value ± standard deviation (SD) or median with an interquartile interval (Q1-Q3). Categorical variables were expressed as absolute values or percentages, and compared by means of the chi-square test. Differences between mean values were verified using the Student's t test when the distribution of variables was normal, in other cases the test Mann-Whitney U or the Kruskal-Wallis Median test were applied. Bivariate correlations were analysed with the Pearson correlation test. P-values below 0.05 were considered significant.

Analyses were performed with Statistica Version 10 (StatSoft, Inc.) and Excel (Microsoft) software.

RESULTS

In our study we found that the median serum 25(OH)D concentration in AMI patients was 7.1 (2.3-13.3) ng/mL and this value was below the recommended reference range for healthy population, Table 2 [10]. Detailed analysis of 25(OH)D levels revealed that 53 patients (89.8%) had vitamin D below 20 ng/mL, and 6 patients (10.2%) had suboptimal 25-(OH)D levels (between 20 and 30 ng/mL). No one reached the optimal level of 25(OH)D above 30 ng/mL.

Among patients with deficiency, 19 had vitamin D levels so low that the results were close to the lower limit of detection of the assay (2.3 ng/mL). Four people were classified into a group of suboptimal supply the body with vitamin D. Interestingly, patients with normoglycemia (NG) had significantly higher vitamin D levels then IGT or DM patients (p=0.01) (Table 2). Additionally, we compared biochemical parameters in those subgroups to see if there are any relevant differences. The only significances were observed in glucose and glycated hemoglobin levels (Table 3).

The most interesting finding of our study is that patients admitted in the beginning of the year (January-March) had lowest vitamin D levels and the highest levels in the end of the

year (October-December) (2.3 (2.3-5.3) vs. 12.3 (8.3-15.2) ng/mL; p=0.007) (Figure 1 A). Consecutively, in the second quarter of the year the median 25-(OH)D was 5.9 (2.3-22.3) ng/mL and in the third one was 8.4 (3.9-14.5) ng/mL (p=0.005). We did not find the differences in 25(OH)D between men and women, nevertheless the tendency to having lower vitamin D levels were observed in women (7.7 (2.3-15.2) vs. 2.3 (2.3-8.7) ng/mL; p=0.11) (Figure 1B). The other interesting observation was that in the first quarter of the year the concentrations of 25(OH)D negatively correlated with glucose levels (r=-0.62; p=0.014). Such relationship was not observed in other seasons.

A tendency in lowering 25-(OH)D levels in STEMI patients in compare to NSTEMI ones was observed (2.3 (2.3-11.3) vs. 8.3 (3.2-14.9) ng/mL; p=0.06). Nevertheless, the seasonal analyses with respect to DM and IGT incidence in STEMI patients was not performed due to the limited patients number.

Overall, in the DM group no correlations between biochemical and epidemiological parameters and 25(OH)D concentrations were found. However, in the IGT group we observed significant correlations between 25(OH)D concentrations and fibrinogen (r=0.70; p=0.034) or triglycerides levels (r=0.72; p=0.029). No correlations were found between sex or BMI.

DISCUSSION

The primary finding of our study is that most of AMI patients have VDD. Furthermore we confirmed our working hypothesis that in AMI patients vitamin D levels are subject to variations, depending on the season. This seasonal effect was so strong that it was observed even in those VDD patients. Additionally we found that hyperglycemic conditions are related with VVD deficiency in AMI group.

Several studies indicated that VDD is a very common finding in populations inhabiting northern latitudes [8,9,17]. This deficiency has been observed despite of common knowledge about vitamin D source and its potential food intake.

In our study we found that 53 patients had vitamin D levels below 20 ng/mL (50 nmol/L) so we can consider that most of AMI population suffer from VDD. Our results are taken in relation to the guidelines prepared for the population of Central Europe. According to the recommendations of prophylaxis of vitamin D deficiency in Poland, the concentration of vitamin D <20ng/ml has been treated as VDD and levels between 20 and 30 ng/mL are characterized as suboptimal, with not sufficient supply the body with vitamin D [10]. Additionally, we may confirm that the distribution of VDD in cardiovascular patients are in

concordance with previous investigation by Goleniewska *at al.* [4], nevertheless we did not check association with the severity of coronary lesions and vitamin D levels.

However, the global recommendations are less restricted. It has been generally accepted that blood 25(OH)D levels below 10 ng/mL (or 25 nmol/L) are qualified as 'deficient', but there is no currently accepted definition for 'optimal' 25(OH)D levels [18]. In Central Europe population the correct target for supplementation is 30-50 ng/mL (75-125 nmol/L)[10], nevertheless the 25(OH)D concentration should exceed 30 ng/mL (75 nmol/L) to maximise the effect of vitamin D on calcium metabolism [18].

Despite a significant vitamin D deficiency in AMI patients we observed the seasonal effect in 25-(OH)D levels, with higher levels in the fourth quarter of the year (October-December) and the lowest in the first one (winter). The seasonal variation of vitamin D serum levels is a common phenomenon in the northern hemisphere at latitudes greater than around 40°N, where sunlight is not intense enough to generate vitamin D synthesis in the skin from October to March [18,19]. We may consider that the seasonal deficit in sunlight during the winter month may specially treat elderly patients with high cardiovascular risk, having more deleterious effect on them [20]. However, no association between vitamin D status and incidence of ischemic heart disease or stroke has been confirmed in general population [21].

VDD has been reported in 2–30% of European adults, increasing in cardiovascular patients to 80% in some studies [2,4, 22,23]. Among factors which accompanied VDD risk, female sex is usually considered as important. In our study we observed the tendency to lower serum 25-(OH)D levels in AMI women then in AMI men ($p=0.11$). Our finding is in concordance with some recent reports showing that gender significantly affects vitamin D status in patients with coronary artery disease (CAD) and female sex is an independent predictor of cardiovascular risk [23,24]. It is essential that in our study patients were not supplemented with vitamin D. In common practice, women in postmenopausal period are prevented against osteoporosis and vitamin D supplementation is recommended. Such substantial deficits in 25-(OH)D levels may be explained with the fact, that patients for this study were recruited 3-5 years ago, from less urbanized region of Małopolska. Currently osteoporosis prevention is more common and patients better controlled and more self-confident with respect of osteoporosis risk.

An interesting association between DM and IGT and low 25-(OH)D levels was documented. Hyperglycaemia is frequently observed in patients with AMI, in our study more than 40% of patients had DM or IGT and hyperglycemic conditions may favourite coagulation properties of blood in AMI [25]. However, it is still unsolved if VDD may impair glucose tol-

erance or if vitamin D supplementation may improve glycaemic control. We may assume that vitamin D fortification or even supplementation would be more beneficial for AMI patients with DM or IGT then for normoglycemic ones.

Concluding, high prevalence of VDD in acute cardiovascular patients should be considered as an additional and interfering risk factor. In patients with previous AMI the monitoring of vitamin D levels due to its supplementation should be taken into account. Those patients with hyperglycemia may be more beneficial after vitamin D supplementation. Additional conclusion is that the vitamin D control (e.g. 25-(OH)D assessment) should be provided for patients at risk to avoid both the over-dosage in vitamin D supplementation or insufficiency.

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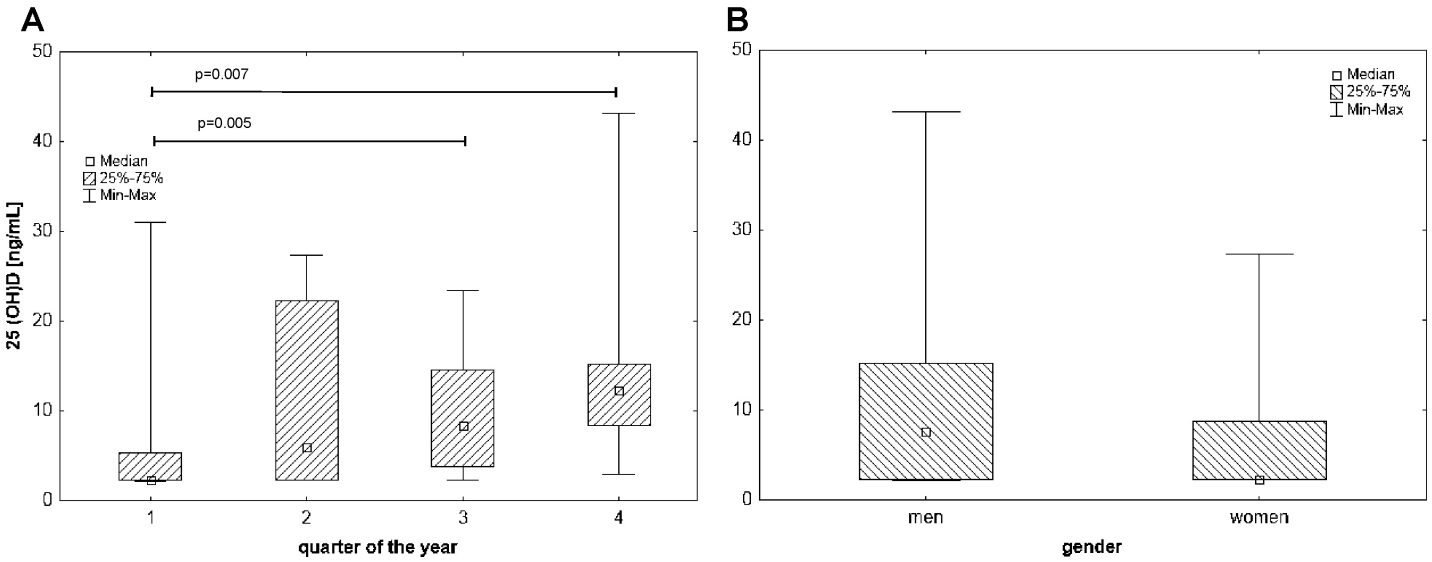
Figure 1. Graphical presentation of median values of vitamin D concentrations in AMI patients during admission to Department of Invasive Cardiology. (**A**) presents seasonal changes: (1) January-March, (2) April-June, (3) July-September and (4) October-December; (**B**) presents gender difference. Number of patient analyzed in the each quarter of the year: n=18 (1); n=10 (2); n=22 (3); n=9 (4). Data are presented as median values with the interquartile interval and minimal-maximal values. Analysis was performed as Kruskal-Wallis median test.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10
0
Median
25%-75%
Min-Max
men
women
gender

Table 1. Characteristics of a study group, and comparison with respect to gender.

	AMI group (n=59)	**Women (n=13)**	**Men (n=46)**	**p**
Age, (yrs)	58 ± 9.4	61 ± 9.8	57.0 ± 9.3	0.75
BMI (kg/m^2)	27.0 (24.6-31.0)	29.0 (26.0-32.8)	27.6 (26.0-31.9)	0.68
current smokers n (%)	37 (62.7)	6 (46.2)	31 (67.4)	0.46
diabetes mellitus n (%)	14 (23.7)	3 (23.1)	11 (23.9)	0.96
IGT n (%)	11 (18.6)	3 (23.1)	8 (17.4)	0.70
arterial hypertension n (%)	47 (79.7)	10 (76.9)	37 (80.4)	0.93
TC (mmol/L)	5.64 ± 1.34	5.92 ± 1.87	5.57 ± 1.16	0.40
LDL-C (mmol/L)	3.84 ± 1.21	3.97 ± 1.78	3.80 ± 1.00	0.60
HDL-C (mmol/L)	1.14 (0.99-1.43)	1.14 (1.05-1.54)	1.18 (0.96-1.41)	0.64
TG (mmol/L)	1.23 (0.83-2.04)	1.17 (0.77-1.45)	1.28 (0.90-2.04)	0.62
glucose (mmol/L)	6.82 (5.90-8.14)	5.27 (4.80-6.30)	6.72 (5.86-8.06)	0.52
HbA1C (%)	6.35 (5.8-7.0)	6.50 (5.9-7.4)	5.8 (5.6-6.4)	**0.048**
creatinine (μmol/L)	78.0 ± 15.77	66.9 ± 10.27	81.3 ± 15.7	**0.003**
fibrinogen (g/L)	3.78 (3.23-4.75)	4.02 (3.53-4.68)	3.74 (3.21-4.75)	0.17
hsCRP (mg/L)	4.10 (1.80-11.54)	6.20 (1.90-18.00)	3.90 (1.80-7.30)	0.12
hs-TnTmax,(ng/L)	66 (30-166)	82 (42-104)	64 (26-260)	0.72

Values are given as mean ± SD or median (Q1-Q3). Abbreviations: BMI, body mass index; hsCRP, high sensitivity C-reactive protein; HbA1C, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 2. Comparing vitamin D concentrations in AMI patients with respect to gender and glucose tolerance.

	AMI group (n=59)	**Women (n=13)**	**Men (n=46)**	**p**
25(OH)D [ng/mL]	7.1 (2.3-13.3)	2.3 (2.3-8.7)	7.7 (2.3-15.2)	0.11[a]
	NG (n=34)	**IGT (n=11)**	**DM (n=14)**	**p**
	9.2 (2.3-16.8)	2.3 (2.3-3.9)	8.5 (2.5-13.3)	**0.01**[b]

Abbreviations: AMI, acute myocardial infarction; DM, diabetes mellitus; IGT, impaired glucose tolerance; NG, normoglycemic patients.

Bold p-values represent statistical significance. [a] women vs. men comparison – Mann-Whitney U test; [b] Kruskal-Wallis median test.

Table 3. Comparing biochemical parameters in AMI patients with respect to glucose tolerance and diabetes.

	NG (n=34)	**IGT (n=11)**	**DM (n=14)**	p
TC (mmol/L)	5.72 (4.98-6.49)	6.37 (3.85-6.90)	5.15 (4.50-5.87)	0.25
LDL-C (mmol/L)	4.02 (3.15-4.39)	4.19 (2.32-4.66)	3.29 (2.81-3.96)	0.17
HDL-C (mmol/L)	1.20 (1.09-1.45)	0.99 (0.94-1.25)	1.16 (0.95-1.45)	0.17
TG (mmol/L)	1.04 (0.74-1.92)	1.47 (1.21-2.21)	1.36 (0.97-2.62)	0.21
glucose (mmol/L)	6.4 (5.7-7.1)	6.72 (6.51-8.29)	8.57 (7.15-10.72)	**0.002**
HbA1C (%)	NA	5.9 (5.8-6.0)	6.5 (6.3-7.4)	**0.03**[a]
creatinine (μmol/L)	76.0 (67.0-86.0)	76.0 (67.0-95.0)	78.0 (70.0-83.0)	0.82
fibrinogen (g/L)	3.83 (3.26-4.75)	4.02 (3.23-4.45)	3.50 (3.15-5.48)	0.91
hsCRP (mg/L)	3.80 (1.60-6.30)	3.90 (2.20-20.60)	4.85 (1.60-11.54)	0.56

Values are given as median (Q1-Q3). Abbreviations: hsCRP, high sensitivity C-reactive protein; DM, diabetes mellitus; HbA1C, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Data analyzed by means of Kruskal-Wallis median test and [a] Mann-Whitney U test, bold p-values represent statistical significance.