ORIGINAL ARTICLE

Obesity and antiplatelet effects of acetylsalicylic acid and clopidogrel in patients with stable angina pectoris after percutaneous coronary intervention

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KEY WORDS

acetylsalicylic acid, aggregometry, clopidogrel, coronary artery disease, obesity

ABSTRACT

INTRODUCTION Obesity is a cluster of medical conditions affecting several pathophysiological processes, including platelet (PLT) function.

OBJECTIVES We evaluated the association between obesity and PLT response to dual antiplatelet therapy over 1 month in patients with stable angina pectoris after percutaneous coronary intervention (PCI).

PATIENTS AND METHODS Patients with stable angina pectoris (n = 130) and prior therapy with acetylsalicylic acid (ASA, 75 mg/d) after PCI were enrolled into the study and divided based on a body mass index (BMI): BMI <25 kg/m² (group A); BMI = 25–29.9 kg/m² (group B); and BMI ≥30 kg/m² (group C). PLT function was assessed by impedance aggregometry 24 hours after PCI and a loading dose (LD) of clopidogrel (CLO, 600 mg) and after 30 days of a maintenance dose (MD) of CLO and ASA of 75 mg/d. The delta values were calculated as the difference between the tests performed 30 days and 24 hours after PCI.

RESULTS The PLT function changed significantly over a 30-day follow-up. The initial PLT reactivity to adenosine diphosphate (ADP1) was lower in group A and was the highest in group C (P <0.05). The PLT reactivity to collagen (COL1) and arachidonic acid was lower in group A (P <0.05) with no differences between groups B and C. There were no differences among the subgroups in PLT reactivity assessed after 30 days. A multivariate regression analysis showed that BMI (P = 0.03), creatinine serum concentration (P <0.01), male sex (P <0.01), and active smoking (P <0.001) are the independent predictors of ΔADP.

CONCLUSIONS Obesity is associated with a lower response to CLO LD but PLT function after 30 days of CLO MD is similar in patients with obesity and normal-weight.

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INTRODUCTION Obesity is a common disease in our clinical practice and a major public health problem. The World Health Organization estimates that over 1.4 billion adults worldwide were overweight and obese in 2008 and that their prevalence is increasing in both developed and developing countries.[1] Obesity is a cause of numerous diseases including dyslipidemia, hypertension, type 2 diabetes, and other cardiovascular diseases (CVD), sleep apnea syndrome, nonalcoholic fatty liver disease, infertility, and some cancers. Despite a well-evidenced increased risk of mortality in obese subjects, several studies have suggested that the relationship between obesity and survival in patients with coronary artery disease (CAD) after percutaneous coronary interventions (PCI) is a U-shaped curve with a steep increase in mortality among underweight (body mass index, BMI ≤20 kg/m² or BMI ≤18 kg/m²) and morbidly obese subjects (BMI ≥40 kg/m²).[2] This phenomenon,

known as the "obesity paradox", was first reported by Ellis et al[3] and confirmed in further studies, including recent large studies.[4-6]

Dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel (CLO) is a gold standard in patients with stable angina pectoris (SAP) after elective PCI with stent implantation.[7] The variability of on-treatment platelet (PLT) reactivity is considered to be a risk factor for recurrent ischemic events, bleeding complications, and the patient's clinical characteristics, including obesity; these outcomes were suggested to be major risk factors of a poor response to antiplatelets, especially CLO.[8-10] Therefore, the conclusions of obesity paradox studies and PLT reactivity studies seem to be inconsistent. Most studies, however, used only 1 time point for the PLT function test, assessed only the short-term effects of CLO loading dose (LD), or enrolled a heterogeneous group of patients with both the LD and maintenance dose (MD) initiated at least 1 week earlier or patients with SAP and acute coronary syndromes (ACS).[11-13]

A large body of evidence supports the major role of inflammation in atherosclerosis.[14] Therefore, several inflammatory biomarkers, including the number of total white blood cells (WBCs) and their subtypes, were found to be associated with CAD progression and cardiovascular risk.[15]

The main purpose of this study was to evaluate the association between obesity and PLT reactivity in response to dual antiplatelet therapy over a 1-month follow-up in patients with SAP after elective PCI.

PATIENTS AND METHODS

Study population A total of 130 consecutive patients with SAP and successful PCI with stent implantation (Thrombolysis in Myocardial Infarction, TIMI 3) were enrolled in the study. Standard pharmacotherapy followed the European Society of Cardiology recommendations[7] with antiplatelets (ASA and CLO, 100% of the patients), statins (100%), β-blockers (95%) and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists (95%) adjusted to heart rate and blood pressure, diuretics (40%), calcium channel blockers (25%), fibrates (15%), oral diabetes drugs (28%), insulin (12%), proton-pump inhibitors (35%), and nitroglycerin (20%). The PLT treatment was similar in all patients, including ASA at a dose of 75 mg/d introduced at least 6 months before hospitalization and CLO at an LD of 600 mg given during the PCI procedure and 75 mg/d starting on the day after the PCI.

The exclusion criteria included ACS, a history of myocardial infarction of less than 6 months before enrollment to the study, acute and chronic inflammatory diseases (in the 3 preceding months or WBC ≥10×10^3/μl or both), current gastrointestinal tract diseases, hormone replacement therapy, hematological disorders (including prior or active bleeding, blood transfusions in the past 5 years, PLT count <100 × 10^3/μl, hematocrit <25%), acute and chronic kidney disease (glomerular filtration rate, <60ml/min/1.73 m^2), underlying malignancies, comorbid psychiatric or neurological disorders, treatment with other antiplatelets, oral anticoagulant therapy, nonsteroidal anti-inflammatory drugs, steroids, or other drugs having potential effects on platelets. All of the subjects provided written informed consent to participate in the study, and the study protocol was approved by the Ethics Committee of the Medical University of Silesia (Katowice, Poland).

Methods All patients underwent a clinical assessment with routine laboratory tests and standard diagnostic tests (electrocardiogram, transthoracic echocardiography). A complete blood count (CBC) with peripheral differential WBC and PLT counts were assessed, and the baseline neutrophil and lymphocyte counts were variables of interest. Anthropometric measurements (body weight, height, and waist circumference [WC]) were measured and the BMI was calculated. The study group was divided into 3 subgroups depending on the BMI: BMI <25 kg/m^2 (group A), BMI = 25–29.9 kg/m^2 (group B), and BMI ≥30 kg/m^2 (group C). Moreover, the definition of metabolic syndrome (MS) by the International Diabetes Federation (IDF) was used for further analysis. MS was diagnosed if the patient had abdominal obesity (a WC of ≥80 cm in women and ≥94cm in men) and 2 of the following: increased triglyceride levels (TG ≥150 mg/dl or treatment), reduced high-density lipoprotein (HDL) cholesterol levels (<40 mg/dl in men and <50 mg/dl in women or treatment), increased blood pressure or specific treatment, increased fasting plasma glucose levels, or diagnosed type 2 diabetes.[16] Compliance with drug treatment was verified at 1 month based on the tablet count, and all patients showed full compliance with ASA and CLO.

Follow-up and clinical events All patients were followed up (12 months after PCI) for cardiovascular mortality, ACS, stent thrombosis (definite = confirmed in angiography / pathology, or probable = any unexplained death within the first 30 days) and cerebral infarction. All of the events were then related to the PLT reactivity results and baseline CBC parameters.

Platelet function assay The analysis of PLT function was performed using a point-of-care whole blood impedance aggregometry, multiple electrode aggregometry (Dynabate, Munich, Germany). Fasting blood samples were obtained in the morning from the cubital vein of supine patients into blood collection tubes, using venipuncture. PLT function was analyzed 24 hours after the PCI and CLO at an LD of 600 mg (1) and 30 days after PCI during an MD of 75 mg of CLO daily (2). We assessed PLT reactivity at both time points during long-term (≥6 months) therapy with ASA (75 mg/d). The delta values were calculated as the differences between MD (2) and LD (1) PLT function tests (change during

1 month). The impedance aggregometry procedure included 300 ml of whole blood and 300 ml of saline, 0.9%, preheated at 37°C and incubated for 180 seconds. Next, 20 ml of the particular agonist solution was added, and the test was performed (6 minutes). The final concentrations of the test solutions were as follows: adenosine diphosphate (ADP), 6.5 mM (ADP test); collagen (COL), 3.2 mg/ml (COL test); arachidonic acid, 0.5 mM (ASPI test); and thrombin receptor activating peptide (TRAP), 32 mM (TRAP test). Effective ASA treatment leads to reduced aggregation in the ASPI and COL tests. The ADP test is sensitive to antiplatelet effects of CLO. We performed the aggregometry analysis at the Department of Hematology and Bone Marrow Transplantation at the Medical University of Silesia, Katowice, Poland. Measurements for each patient were conducted with the same kit to avoid inter-kit variability (intraassay variability <5%).

Statistical analysis The results were expressed as means ± standard deviation for normally distributed variables or number and percentage. Variables with a normal distribution were analyzed with the Kolmogorov–Smirnov test. Baseline clinical parameters and the measures were compared between the subgroups using the analysis of variance (ANOVA) test. The change of PLT function tests over the time was analyzed as repeated--measures ANOVA. Associations between parameters were assessed using the Pearson or Spearman correlation analysis, depending on the parametric or nonparametric variables. Multivariate logistic and linear regression analyses were used to assess independent predictors of delta values. A *P* value of less than 0.05 was considered statistically significant. The sample size was not calculated a priori. We performed post hoc calculations, which showed that the study had a power of 80%, with a 2-sided α-value of 0.05, to detect different PLT functions assessed in the ADP and COL tests. A statistical analysis was performed using the MedCalc software for Windows (MedCalc, version 12.5, Ostend, Belgium).

RESULTS

Study population and baseline characteristics The clinical characteristics of the patients and the baseline parameters of WBC and PLT are presented in TABLE 1 and Supplementary material online, *Table S1*. In brief, our study group (n = 130) included mostly men (60%) with typical cardiovascular risk factors: hyperlipidemia (100% of the patients), hypertension (92%), diabetes (31%), overweight (34%), and obesity (46%). Most of the patients (77%) fulfilled the IDF's definition of MS. Normal-weight patients (age, 65.1 ±9.9 years) were mostly men (57% of the patients) with hyperlipidemia (100%), hypertension (69%), diabetes (15%), and the status of active smokers (19%). As expected, individuals included in the overweight and obesity groups (group B, 64.2 ±9.2 years; group C, 65.2±9.1 years) were also mostly men (64% vs 60%) with high rates of such risk factors as hyperlipidemia (100%), hypertension (93% vs 98%), diabetes (25% vs 43%), and active smoking (14% and 17%).

TABLE 1 Baseline clinical characteristics of the patients

age, y		64.7 ±9.4
women / men		52 (40) / 78 (60)
hypertension		120 (92)
diabetes		40 (31)
hyperlipidemia		130 (100)
triglycerides, mg/dl		142.6 ±71.3
total cholesterol, mg/dl		170.1 ±42.7
LDL cholesterol, mg/dl		96.6 ±36.5
HDL cholesterol, mg/dl		45.6 ±14.6
current smoking		20 (15)
waist, cm		101.9 ±11.3
hip, cm		102.5 ±8.4
waist-to-hip ratio		0.99 ±0.1
BMI, kg/m^2	20.0–24.9	26 (20)
	25.0–29.9	44 (34)
	30.0–40.0	60 (46)
metabolic syndrome		100 (77)
ejection fraction, %		56.8 ±8.6

Data are presented as mean ± standard deviation or number (percentage) of patients.

Conversion factors to SI units are as follows: for triglycerides, –0.01129; for total cholesterol, HDL cholesterol; for LDL cholesterol, –0.02586.

Abbreviations: BMI, body mass index; HDL, high--density lipoprotein; LDL, low-density lipoprotein

Loading dose and maintenance dose platelet reactivity The mean LD values of PLT tests performed 24 hours (1) and 30 days after the PCI (2) are presented in FIGURE 1. The ADP (P <0.001), COL (P <0.001), and TRAP (P <0.001) tests were significantly increased 30 days after PCI in the study group (FIGURE 1). The LD (1) or MD (2) PLT reactivity to ASA or CLO (ADP, COL, and ASPI tests) was not associated with age or sex.

Platelet reactivity and body mass index The study group was divided based on the BMI: BMI <25 kg/m^2 (group A); BMI = 25–29.9 kg/m^2 (group B); and BMI ≥30 kg/m^2 (group C). The LD PLT reactivity to ADP (ADP1) was significantly different between the subgroups, with the lowest reactivity in group A and the highest—in group C. PLT reactivity to COL (COL1) and ASPI (ASPI1) was significantly lower in group A, with no differences between groups B and C. However, there were no significant differences between the subgroups in terms of PLT reactivity assessed after 30 days (FIGURES 2A–C). Moreover, the mean difference between the MD (2) and LD (1) PLT reactivity to ADP (ΔADP) was significantly inversely associated with both BMI and WC (FIGURES 3AB). A multivariate regression analysis showed that

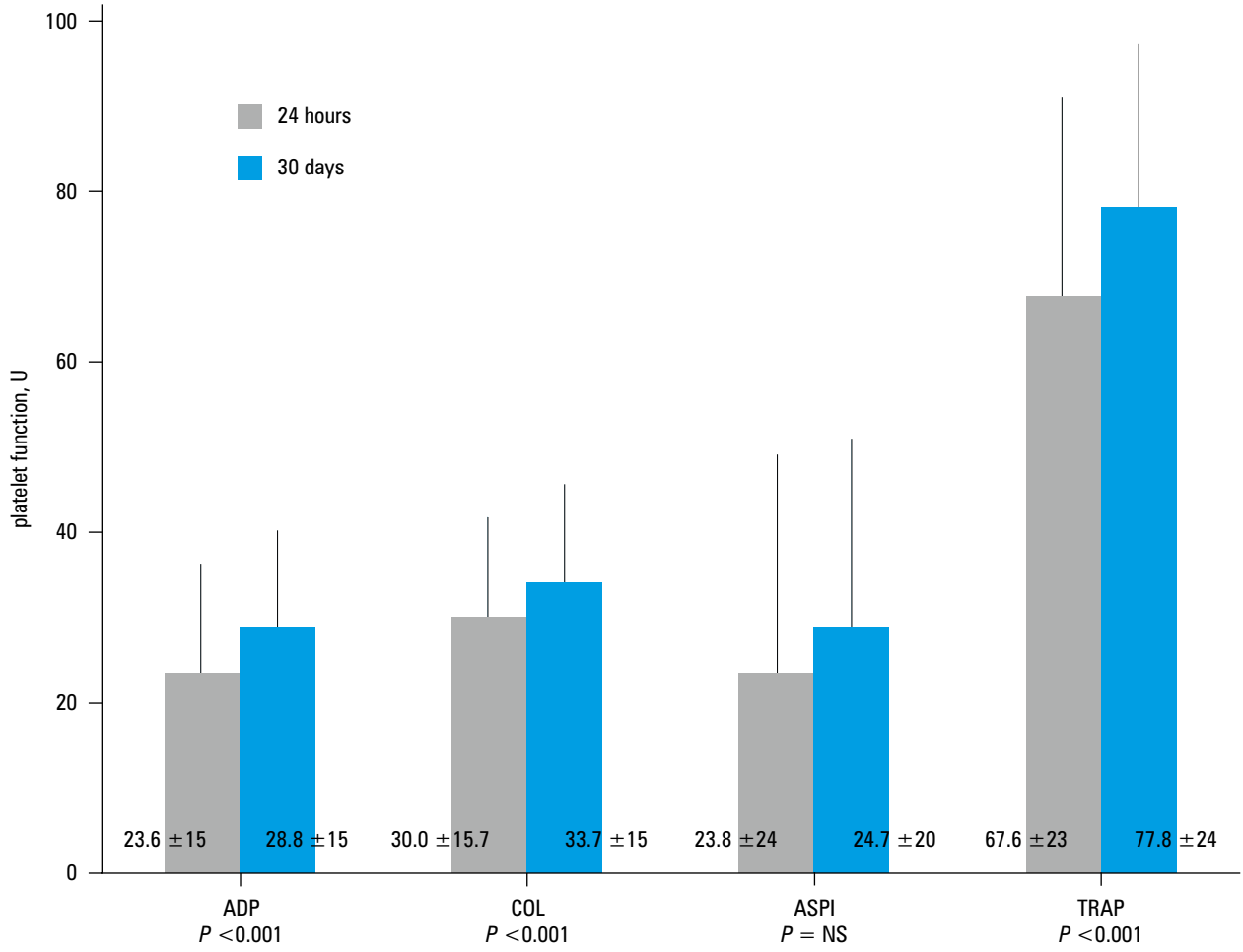


FIGURE 1 Mean values of platelet function tests performed 24 hours after percutaneous coronary intervention with a loading dose and during a maintenance dose of clopidogrel (both time points during a maintenance dose of acetylsalicylic acid) Abbreviations: ADP, adenosine diphosphate; ASPI, arachidonic acid; COL, collagen; NS, nonsignificant; PCI, percutaneous coronary intervention; TRAP, thrombin receptor-activating peptide; others, see TABLE 1

BMI, creatinine serum concentration, male sex, and active smoking are independent predictors of ΔADP (TABLE 2).

Baseline white blood cells and platelet function PLT test reactivity to ADP was significantly associated with the lymphocyte count (ADP1: $r = 0.42$, $P < 0.001$; ADP2: $r = 0.36$, $P < 0.001$) and inversely correlated with the neutrophil-to-leukocyte ratio (ADP1: $r = -0.22$, $P = 0.03$; and ADP2: $r = -0.23$, $P = 0.03$). The baseline WBC count also revealed a significant correlation with the ADP1 test result ($r = 0.22$, $P = 0.04$); neutrophil count was not associated with PLT reactivity to CLO (Supplementary material online, *Table S2*).

Follow-up and clinical events During the follow-up (12 months after PCI), there were 4 deaths (2 cardiovascular deaths), 5 patients had ACS, and 1 patient had cerebral infarction (see the Supplementary material online, *Table S3*, for the results of PLT tests). None of the patients had a definite or probable stent thrombosis. Owing to the low number of clinical endpoints, further statistical analysis did not include an association between PLT function and clinical events.

DISCUSSION Our study showed significant and complex associations between obesity and on-treatment PLT function in patients with SAP. Although the PLT response to an LD of CLO was worse in overweight and obese patients compared with normal-weight patients, it significantly increased during 1 month of treatment with no BMI-related differences in terms of chronic CLO treatment. PLT response to a long-term therapy with ASA was better in lean subjects, with no differences between overweight and obese patients. Despite the variability in PLT function, there were no episodes of stent thrombosis in a 1-year follow-up; due to a relatively low number of incidences, clinical events were not included in the analysis.

Our study provides novel data on the complex and biphasic relationship between PLT function and obesity. Although overweight and obesity is associated with a worse PLT response to a CLO LD, further PLT reactivity after 1 month is not dependent on BMI. Our results provide another explanation supporting similar or even better clinical outcomes in CAD after PCI (obesity paradox). Moreover, we showed that PLT response to a CLO LD represents only initial PLT function and should not be referred to in later weeks of antiplatelet therapy.

Antiplatelet drugs, including ASA and CLO, play a well-established and fundamental role in cardiovascular pharmacotherapy, especially in patients who have received a stent implantation. Unfortunately, their effectiveness is heterogeneous; recent studies have revealed an association among residual on-treatment PLT reactivity

("resistance"), stent thrombosis, and cardiovascular outcomes.[17-19] The rate of patients with high on-treatment reactivity varies among studies and depends on the definitions; it ranged between 4% and 30% for CLO[20] and between 5% and 65% for ASA.[21] There are several acquired and inherent risk factors of on-treatment ASA or CLO resistance, including typical cardiovascular risk factors, inflammatory disorders, drug interactions, genetic factors, and poor compliance.[17] Novel drugs (prasugrel, ticagrelor) show stronger antiplatelet effects and may overcome CLO resistance in most patients.[11,22] However, these drugs also have a higher risk of bleeding complications; except for selected high-risk patients, ASA and CLO are still recommended for SAP patients after PCI by the current guidelines of the European Society of Cardiology.[7]

Obesity and platelet function Our findings of significant differences in PLT response to an LD of CLO depending on the BMI category are consistent with the results of previous reports.[23-27] However, despite statistical significance, some studies found very low correlation coefficients between BMI and PLT reactivity, which could also be interpreted as a very low clinical significance.[28] Gaglia et al[28] found a poor association between BMI and PLT reactivity and no association with high on-treatment PLT reactivity based on different PLT function tests (VerifyNow P2Y12, vasodilator-stimulated phosphoprotein phosphorylation, and light transmission aggregometry). However, the PLT tests were performed 6 to 24 hours after PCI in a heterogeneous group of CAD patients on dual antiplatelet therapy (CLO LD or MD and ASA LD).[28]

A great majority of previous studies assessed only a post-LD PLT reactivity and used it as an equivalent for the overall on-treatment PLT response.[12,23-26,28-30] In most cases, the initial (LD) and chronic (MD, usually after 1 month) response to CLO were dissimilar.[31,32] Darlington et al[13] found that although the LD of prasugrel (60 mg) improved antiplatelet effects compared with high-dose clopidogrel (900 mg) in obese nondiabetic patients, PLT reactivity on an MD (10 vs 150 mg/d) was similar.[13] Our results are in agreement with those observations and highlight the need for repeat PLT function testing during chronic antiplatelet therapy. Pankert et al[33] showed that PLT response to an MD of CLO (75 mg or 150 mg/d) or prasugrel (10 mg/d) is associated not only with the BMI category, but also with metabolic dysfunction based on the clinical criteria of MS. Moreover, there were no significant differences in PLT response to thienopyridines between obese patients without MS and nonobese patients. A large majority of our patients had MS; therefore, we could not compare their PLT function with non-MS obese subjects.

PLT aggregation after an LD of CLO was associated with 30-day clinical outcomes in patients scheduled for elective PCI.[29] Moreover, Wang et al[30] showed that suboptimal on-clopidogrel PLT reactivity is an independent predictor of the composite endpoint at 1-year follow-up, with a significantly increased prevalence of diabetes in the clopidogrel-resistant group and only borderline differences in terms of BMI ($P = 0.049$). However, most importantly, PLT function evaluated after 1-month follow-up was the main predictor of further clinical outcomes at 1-year follow-up.[32]

Although increased PLT reactivity in obese and diabetic patients was identified using different methods,[34] evidence regarding the exact mechanisms linking obesity and PLT function is scarce. Patients with higher body weight (≥60 kg) showed decreased levels of CLO active metabolite compared with those with lower body weight (<60 kg).[35] In patients with diabetes, the impaired PLT response to CLO is largely explained by the altered pharmacokinetics of the drug and a modestly impaired P2Y12 signaling pathway.[12] Major pathomechanisms responsible for the suboptimal effect of either thienopyridines or ASA in obese patients with MS include increased PLT turnover, increased exposure to ADP, impaired synthesis and action of cyclic nucleotides in PLT, increased cytosolic calcium, and reduced activity of CYP3A4 (cytochrome P450).[33,36,37]

Given that the vast majority of patients with diabetes do not meet recommended treatment goals for lipid and glucose levels or arterial pressure,[38] an improvement in optimal CV pharmacotherapy may also improve the effects of antiplatelets in this group of patients. Moreover, the increased mean platelet volume and higher levels of reticulated PLT (not confirmed in our study) and enhanced levels of PLT trigger proinflammatory and prothrombotic cytokines or oxidative stress; these effects were also suggested to be involved in the background of PLT hyperactivity in obese patients.[39] Finally, an impaired response to antiplatelets could be a simple consequence of underdosing and reduced bioavailability. However, increasing the dose of CLO or ASA significantly increased the risk of bleeding and failed to overcome resistance in most subjects.[26,33] Moreover, a novel antiplatelet, ticagrelor, was found to have similar efficacy independent of BMI and obesity, suggesting that other mechanisms are also involved in high on-treatment PLT reactivity.[22] Therefore, drug underdosing or physiological variations in drug response seem to be minor factors.[39]

Several studies used different PLT function tests for individualized and tailored antiplatelet therapy with P2Y12 blockers providing mixed results.[33] Therefore, current guidelines do not recommend the routine use of PLT tests for all patients, suggesting their value only in selected cases.[7] Although obese individuals should benefit from recently introduced and more aggressive novel antiplatelets, CLO is still the drug of choice for patients after elective PCI. It seems that traditional cardiovascular risk factors and genetic predisposition account only for a part of

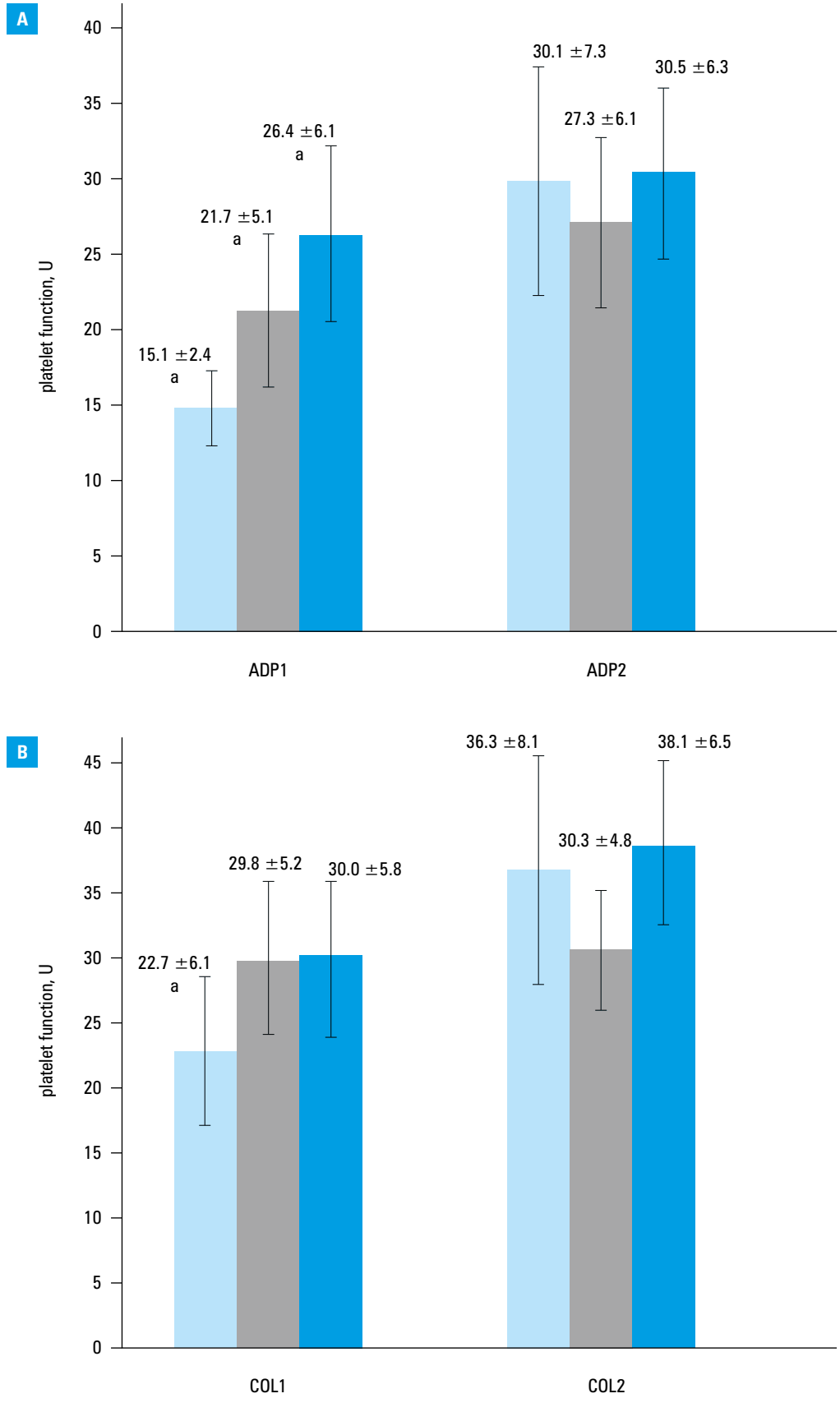


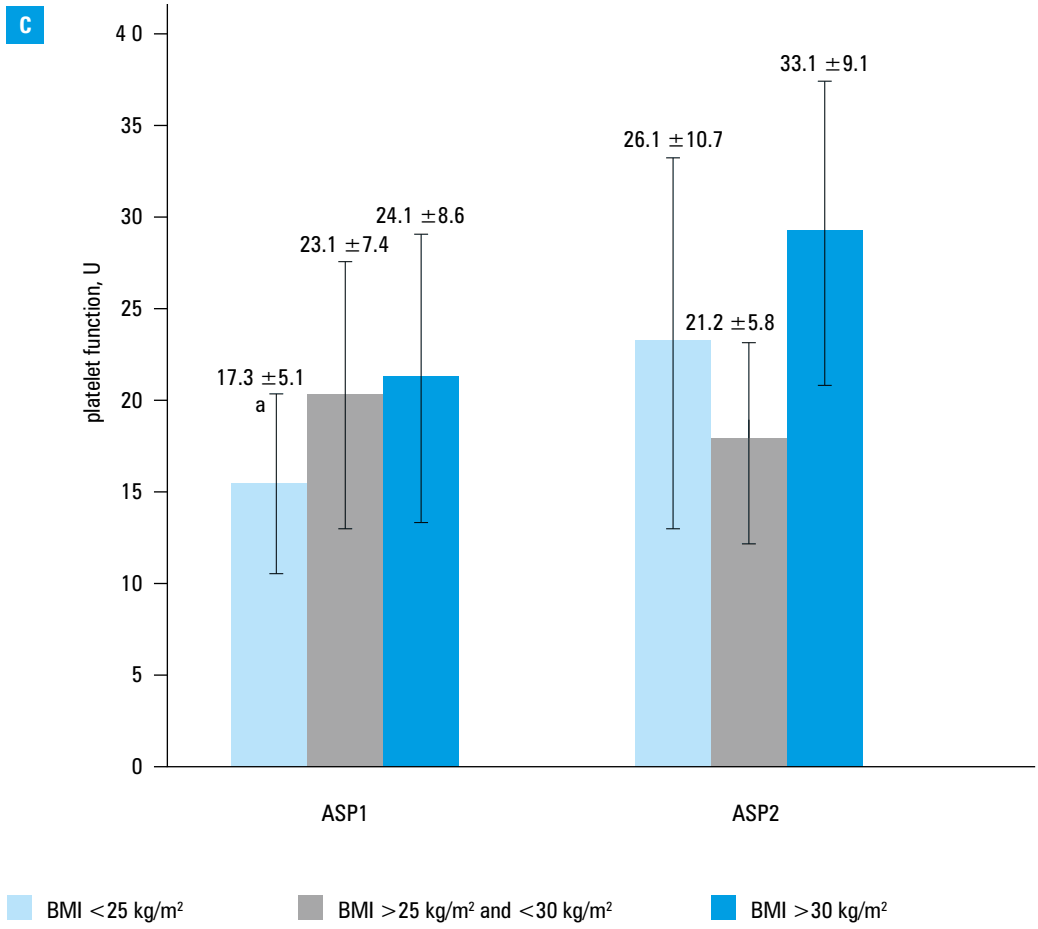
FIGURE 2 Platelet reactivity to clopidogrel (ADP test) (**A**) and acetylsalicylic acid (COL and ASPI) (**B**, **C**) assessed 24 hours after percutaneous coronary intervention with a loading dose (ADP1, COL1, ASPI1) and during a maintenance dose (ADP2, COL2, ASPI2) of clopidogrel (both time points during a maintenance dose of acetylsalicylic acid) according to body mass index

a $P < 0.05$

Abbreviations: see **TABLE 1** and **FIGURE 1**

the variability in PLT reactivity, and additional research is necessary.

Obesity paradox The results of a meta-analysis including 22 studies (10 with subjects scheduled for PCI) that enrolled 214 278 patients with CAD revealed a lower risk of short- and long-term mortality after PCI among obese individuals compared with normal-weight subjects.[40] In addition, a meta-analysis of 11 prospective randomized studies showed a lower risk of mortality and CVD events among obese subgroups during a 2.1-year follow-up. All of the studies included in this meta-analysis excluded subjects with terminal illnesses and malignancies.[41] Moreover, the results of a meta-analysis including 6 studies (15 923 patients with



CAD) revealed that the mortality risk was directly proportional to WC and inversely proportional to BMI.[42]

Our study revealed a significant association between PLT reactivity and the indices of both obesity (BMI) and central obesity (WC). There are several arguments for and against the obesity paradox in CVD, and the major potential explanations include suboptimal methods of the studies, various clinical phenotypes of being overweight and obese, metabolic status and cardiopulmonary fitness, and, finally, early aggressive treatment.[43] We showed that obese subjects do not have poorer PLT responses to chronic antiplatelet treatment, as might be expected. Differences in on-treatment PLT reactivity should not be used to explain the clinical outcomes between lean and obese patients after elective PCI. Moreover, given that the large majority of patients discharged from cardiology departments after PCI have optimal cardiovascular drugs, the argument for using a more aggressive pharmacotherapy for obese patients is not valid.

Baseline white blood cells and platelet function O'Donoghue et al[44] showed that the baseline neutrophil count is a strong and independent predictor of cardiovascular death and heart failure in patients with ST segment-elevated myocardial infarction and that the benefits of clopidogrel are diminished in patients with increased neutrophil levels. We found that the total WBC count at baseline is associated with PLT reactivity only when assessed in response to an LD of CLO with no associations with MD PLT reactivity, suggesting that the baseline WBC count adds predictive value only for initial PLT function tests in patients with stable CAD. However, a significant association was found between the baseline lymphocyte count and both initial and control PLT function tests. The total WBC count and PLT parameters obtained in routine CBC were not predictive of PLT activity in our study group. Recent studies have provided results on the predictive value of lymphocytopenia in patients with ACS or heart failure as a marker of neurohormonal activation. However, it was not confirmed in patients with stable CAD compared with controls.[45] Our results suggest that lymphocytes are either involved in the PLT response to initial and chronic therapy with thienopyridines or that the lymphocyte count may be a more sensitive marker of immune activation in patients with stable CAD.

Limitations and conclusions The main limitations of our study include a relatively low number of patients and the lack of genetic testing for polymorphisms, which might have also affected PLT function. We have chosen one of the most reliable and frequently used methods of PLT function assessment, although we did not use alternative or additional methods. Moreover, our study design did not include the initial PLT activity before an LD of CLO, which would provide additional data.

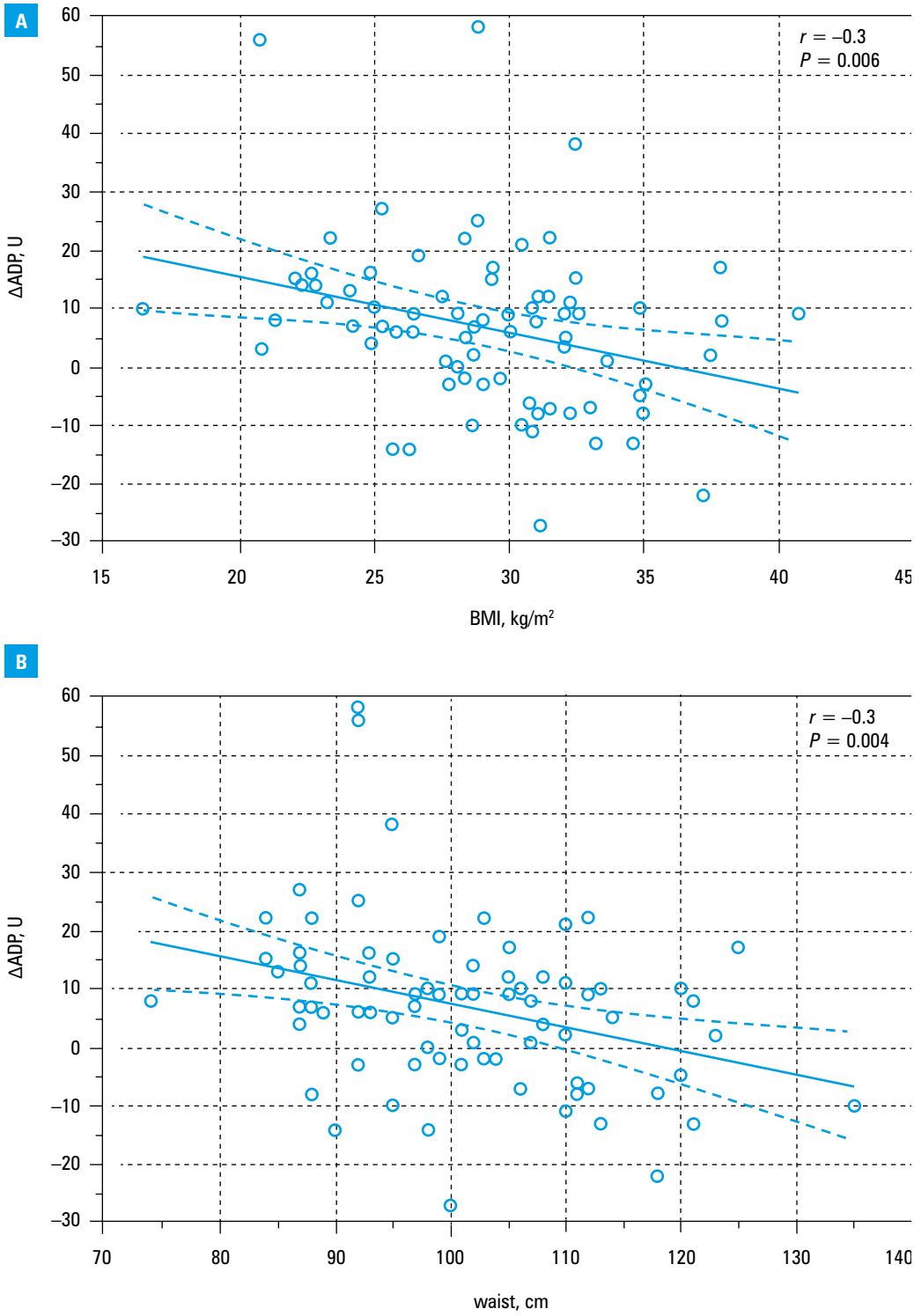


FIGURE 3 Platelet reactivity to clopidogrel during 1 month (ΔADP = ADP2–ADP1) and body mass index (**A**) or waist circumference (**B**). Abbreviations: ADP1, adenosine diphosphate-dependent platelet function 24 hours after 600 mg of clopidogrel; ADP2, adenosine diphosphate-dependent platelet function assessed after 1-month therapy with clopidogrel (75 mg/d); see **TABLE 1**

Finally, given the differences in the clinical phenotypes of obesity, future studies should also focus on a more detailed assessment of obesity, using alternative methods of fat quantification or evaluation of metabolic dysfunction.

We enrolled a population of patients with stable CAD after elective stent implantation with similar pharmacotherapies and PLT tests conducted at 2 time points. Our study adds to the current data that there is a complex association between obesity and cardiovascular risk and pharmacotherapy.

In conclusion, we found that although obesity is associated with an impaired PLT response to an LD of CLO, further PLT reactivity during a chronic MD of CLO and chronic therapy with ASA are similar among obese and normal-weight subjects.

Contribution statement All authors conceived the idea of the study. MH and BL were involved in data collection. MH analyzed the data and edited the manuscript. KMS, SKK, and ZG analyzed the data and approved the final version of the manuscript.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

TABLE 2 Multivariate regression analysis: platelet function during 1 month (ΔADP = ADP2–ADP1) and risk factors

Parameter	ΔADP			
	β	95% CI		*P* value
age	0.38	–0.05	0.81	0.09
male sex	–11.5	–19.7	–3.3	<0.01
hypertension	2.2	–11.54	15.94	0.75
diabetes	–8.1	–16.2	0.03	0.05
creatinine	16.48	5.56	27.4	<0.01
LDL cholesterol	0.01	–0.09	0.11	0.85
HDL cholesterol	0.17	–0.12	0.46	0.25
triglicerydes	0.04	–0.02	0.09	0.17
smoker	1.42	0.98	1.85	<0.001
BMI	–1.1	–2.07	–0.13	0.03

Abbreviations: CI, confidence interval; others, see **TABLE 1** and **FIGURE 3**

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ARTYKUŁ ORYGINALNY

Otyłość a efekty przeciwpłytkowe u pacjentów z dławicą piersiową stabilną i terapią kwasem acetylosalicylowym oraz klopidogrelem po przezskórnej angioplastyce wieńcowej

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SŁOWA KLUCZOWE

agregometria, choroba wieńcowa, funkcja płytek, klopidogrel, kwas acetylosalicylowy, otyłość

STRESZCZENIE

WPROWADZENIE Otyłość charakteryzuje się licznymi nieprawidłowościami, które wpływają na wiele procesów patofizjologicznych, w tym na funkcję płytek krwi (*platelet* – PLT).

CELE Celem badania była ocena związku pomiędzy otyłością a odpowiedzią PLT na podwójną terapię przeciwpłytkową u pacjentów ze stabilną dławicą piersiową po przezskórnej interwencji wieńcowej (*percutaneous coronary intervention* – PCI).

PACJENCI I METODY Pacjenci z dławicą piersiową stabilną (n = 130) i przewlekłą terapią kwasem acetylosalicylowym (ASA, 75 mg/d) po PCI zostali włączeni do badania i podzieleni na podstawie wskaźnika masy ciała (*body mass index* – BMI) na trzy grupy: BMI <25 kg/m^2 (grupa A), BMI = 25–29,9 kg/m^2 (grupa B) i BMI ≥30 kg/m^2 (grupa C). Ocena aktywności PLT została przeprowadzona metodą agregometrii impedancyjnej 24 h po PCI i dawce nasycającej klopidogrelu (CLO, 600 mg), a następnie po 30 dniach terapii dawką podtrzymującą (ASA + CLO, 75 mg/d). Wartości delta stanowią różnicę pomiędzy wynikami testów wykonanych 30 dni i 24 h po PCI.

WYNIKI Aktywność PLT zmieniła się znamiennie w okresie 30-dniowej obserwacji. Początkowa reaktywność PLT po adenozynodifosforanie (ADP1) była mniejsza w grupie A i największa w grupie C ($p < 0,05$). Reaktywność PLT po kolagenie (COL1) i kwasie arachidonowym była mniejsza w grupie A ($p < 0,05$) i bez różnic pomiędzy grupami B i C. Ocena funkcji PLT po 30 dniach nie wykazała różnic pomiędzy podgrupami. Analiza metodą regresji wieloczynnikowej wykazała, że BMI ($p = 0,03$), osoczowe stężenie kreatyniny ($p < 0,01$), płeć męska ($p < 0,01$) i nikotynizm ($p < 0,001$) są niezależnymi predykatorami ΔADP.

WNIOSKI Otyłość jest związana z mniejszą odpowiedzią PLT na dawkę nasycającą klopidogrelu, ale funkcja PLT oceniana po 30 dniach terapii dawką podtrzymującą leku jest podobna u pacjentów z otyłością i prawidłową masą ciała.

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