Platelet inhibition by low-dose aspirin is not influenced by body mass or weight

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Abstract
Aspirin’s clinical efficacy may be influenced by body weight and mass. Although inadequate platelet inhibition by aspirin is suggested as responsible, evidence for this in non-diabetic patients is sparse. We investigated the influence of body weight and mass on aspirin’s inhibition of platelet aggregation in healthy adults without diabetes. Cohort one (NYU, n = 84) had light transmission aggregometry (LTA) of platelet-rich plasma to submaximal adenosine diphosphate (ADP) and arachidonic acid (AA) before and following 1 week of daily 81 mg non-enteric coated aspirin. Subjects in the validation cohort (Duke, n = 66) were randomized to 81 mg or 325 mg non-enteric coated aspirin for 4 weeks, immediately followed by 4 weeks of the other dose, with LTA to submaximal collagen, ADP, and AA before and after each dosage period. Body mass index (BMI) range was 18.0–57.5 kg/m² and 25% were obese. Inhibition of platelet aggregation was similar irrespective of BMI, body weight and aspirin dose. There was no correlation between platelet aggregation before or after aspirin with BMI or body weight. Our data demonstrate that aspirin produces potent inhibition of direct and indirect COX1-mediated platelet aggregation in healthy adults without diabetes regardless of body weight or mass – suggesting that other mechanisms explain lower preventive efficacy of low-dose aspirin with increasing body weight/mass.

Keywords
Aspirin, body weight, cyclooxygenase 1, obesity, platelet aggregation

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Introduction
As the obesity epidemic proceeds largely unabated, there is a pressing need to assess the efficacy of many drugs in patients with increasing body weight. Obesity is an independent risk factor for atherosclerotic cardiovascular disease and improved therapeutic strategies to better manage cardiovascular risk in obesity are needed.⁴ Optimal dosing of cardiovascular medications in individuals with high body weights is an underinvestigated area [2], and might allow for improved outcomes.

While aspirin is frequently used to prevent cardiovascular events, a meta-analysis of 10 studies and 117,279 participants found that the clinical benefits of aspirin doses are affected by weight and body mass [3]. Aspirin doses of <100 mg (commonly referred to as “low-dose” within cardiovascular medicine) were effective at primary prevention of major adverse cardiovascular events only in those weighing <70 kg, whereas doses >300 mg exhibited increasing efficacy at body weight >70 kg. Although four decades ago Patrono and colleagues demonstrated that less than 0.5 mg/kg aspirin is adequate to effectively inhibit platelets in healthy individuals [4], some subsequent studies have suggested that obesity is associated with incomplete platelet inhibition by aspirin [5–10]. However, these studies are limited by several factors. First, many tested enteric-coated aspirin, a formulation not recommended clinically due to lack of gastrointestinal protection vs regular aspirin and inconsistent absorption [6–8,11,12]. Additionally, other studies have included heterogeneous samples of individuals with obesity with and without comorbidities such as diabetes which is known to cause impaired responsiveness to aspirin [13]. These shortcomings prevent an accurate assessment of the effect of body weight or mass specifically on low-dose asprin’s efficacy in inhibiting platelet aggregation.

In the present study, we sought to directly assess the influence of body mass and weight on aspirin’s inhibition of platelet aggregation in two separate cohorts of healthy adults.

Methods
This manuscript describes retrospective analyses of existing data from clinical cohorts at two academic medical centers [14–16]. Healthy individuals between 30 and 75 years of age, without cardiovascular disease, diabetes, hypertension or hypercholesterolemia and not taking medications known to influence platelet activity were recruited from NYU Langone Health and Duke University Medical Center under protocols approved by each institution’s IRB (NYU – 10-00607, Duke - Pro000048621). Additional exclusion criteria have been published previously [14–16]. As described [14], subjects in the primary cohort (NYU) underwent fasting blood draws for platelet aggregation

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assessment prior to and following 1 week of 81 mg non-enteric coated aspirin daily. Subjects avoided intense exercise and tobacco use prior to blood draws. Subjects in the validation cohort (Duke) attended a baseline visit and were then randomized to 81 mg or 325 mg non-enteric coated aspirin for 4 weeks, immediately followed by 4 weeks of the other dose of aspirin (Supplemental Figure S1) [15]. Platelet aggregation was assessed before any therapy and after each four-week aspirin dosage period.

Patients in both cohorts had blood collected with sodium citrate (after a 3c discard) and light transmission aggregometry (LTA) was performed, as described [15,17], on platelet-rich plasma within 2 hours of phlebotomy. Complete blood counts including MPV were performed using Sysmex (Mundelein, Illinois, USA) hematology analyzers. The primary cohort underwent LTA using 2 µM adenosine diphosphate (ADP) and 1.5 mM arachidonic acid (AA). Existing LTA data from the validation cohort for 5 µg/mL collagen, 2 µM ADP, and 0.5 mM AA was gathered for this analysis.

We performed analyses stratified by both body mass index (BMI; ≤25 kg/m², 25–30 kg/m², >30 kg/m²) and body weight (≤70 kg, 70–90 kg, >90 kg). The characteristics of subjects within body mass and weight categories were compared with Kruskal Wallis tests and Jonckheere-Terpstra tests for trend. Platelet aggregation data are represented as medians with 25th and 75th percentiles. Comparisons of aggregation across BMI and body weight categories were performed with the Jonckheere-Terpstra test and within categories with the Wilcoxon signed ranks test. Pearson correlation analyses were performed between aggregation pre- and post-aspirin, changes in aggregation, and percent inhibition to aspirin with age, BMI and body weight. Comparisons of platelet inhibition with aspirin by sex were performed using Mann-Whitney U tests. A p-value <0.05 was set a priori as the criterion for statistical significance.

Results

The primary cohort consisted of 84 participants (Table I). Mean age was 36 ± 14 years, 46.4% were female, and 42.9% reported race/ethnicity other than non-Hispanic White. Average BMI was 23.8 kg/m² [interquartile range; 22.0, 25.9] and mean body weight was 70.8 kg [59.2, 78.0]. Twenty-four participants in this cohort were overweight (BMI 25–29.9 kg/m²) and 6 were obese (BMI ≥ 30 kg/m²). Both direct and indirect measures of COX1-mediated platelet aggregation were inhibited by aspirin. In this cohort, 81 mg aspirin daily for 1 week inhibited platelet aggregation to 1.5 mM AA and 2 µM ADP, by 84% [68, 91] and 30% [21, 42], respectively (p < .001 for both comparisons). There was no difference in inhibition of platelet aggregation by aspirin between men (85% [68, 92] and 31% [8, 42]) and women (83% [67, 91] and 29% [20, 42]). Further, there was no association between age and percent of platelet inhibition to either AA (r = −0.09, p = .54) or ADP (r = 0.10, p = .38). Inhibition of platelet aggregation was similar irrespective of BMI and body weight category (Figure 1, Table II). Accordingly, when assessed as continuous variables, there was no correlation between BMI or body weight, platelet aggregation before or after aspirin, the degree of platelet inhibition by aspirin, nor change in urinary thromboxane, soluble CD40 ligand or soluble P-selectin (Supplemental Table S1).

Among 66 participants in the validation cohort, average age was 44 ± 10 years, 36.4% were female, and 54.6% were non-Hispanic White (Table I). Average BMI was 29.7 kg/m² [25.3, 35.8] and body weight was 85.7 kg [70.9, 104.1]. Half were obese and 28.8% were overweight. When subjects were treated with 81 mg aspirin daily, platelet aggregation to 0.5 mM AA, 2 µg/mL collagen or 5 µM ADP was inhibited by 97% [95, 98], 60% [42, 71] and 15% [2, 28], respectively (p < .001 for all comparisons). Higher dose (325 mg) aspirin produced similar inhibition of platelet aggregation: 96% [95, 97], 62% [40, 81] and 19% [3, 30] (p < .001 for all). Responses to aspirin were consistent across body weight and BMI categories (Figure 2, Table III), with no association of either anthropometric measure with platelet aggregation or inhibition (Supplemental Table S2). Consistent with the primary cohort, sex and age did not influence percent inhibition of platelet aggregation in the validation cohort.

Discussion

Our data demonstrate that aspirin produces potent inhibition of platelet aggregation to AA in addition to significant indirect COX1-mediated aggregation to ADP and collagen in healthy men and women. Using data from two independent cohorts employing direct assessment of platelet aggregation with LTA, a reliable measure of platelet-specific effects of aspirin, our study suggests no significant association of body weight and mass with direct and indirect COX1-mediated platelet aggregation. Moreover, the consistency of the results across two cohorts and different doses of aspirin and concentrations of agonists, and whether body weight/mass were assessed as either categorical or continuous variables, suggest little, if any, effect of body weight or mass on the capacity of low-dose aspirin to inhibit direct and indirect COX1-mediated platelet aggregation.

These data may appear to contradict the prevailing literature that low-dose aspirin produces less platelet inhibition in obese individuals [3,5–10]. However, in reality, an independent association of body weight/mass with platelet inhibition by preventive aspirin regimens has not been previously demonstrated. Early studies reporting “incomplete” platelet COX1 inhibition to aspirin with increasing body weight studied enteric-coated aspirin [5–8]. Enteric-coated aspirin resists dissolution in the stomach and releases aspirin in the small intestine. In obesity, greater amounts of intestinal esterases degrade aspirin and impair systemic availability of the enteric-coated form [11]. Findings in studies with enteric-coated aspirin thus cannot be extrapolated to the activity of regular aspirin, which is preferred for the prevention of cardiovascular events as both forms are associated with similar risks of gastrointestinal bleeding [18].

While some studies employing non-enteric coated aspirin suggest reduced COX1 inhibition with increasing body weight, the data are not without significant limitations. In 900 patients with
stable coronary artery disease taking 75 mg regular aspirin daily, BMI >30 kg/m² was associated with greater whole blood aggregation to 1 mM AA in non-adjusted and multivariable regression analyses. However, BMI was not associated with aggregation to collagen, and diabetes had larger impacts on aggregation to both AA and collagen than did BMI[9]. Further, as no measures off of aspirin were made in this study, the inhibition of platelet aggregation was not directly assessed and all subjects demonstrated >95% inhibition of platelet COX1 as measured by serum TXB₂ level [9].

The largest assessment of the effect of aspirin on platelet aggregation by obesity status was in GeneSTAR [10]. This study compared nearly 1200 obese and over 800 non-obese subjects. There was a 4.9% non-zero aggregation rate to 0.5 mM AA in non-obese vs 8.3% in obese subjects taking 81 mg aspirin. However, the authors did not present average percent aggregation on aspirin – an important consideration, as “complete” inhibition of platelets is not considered to require zero aggregation. Additionally, while stratified by BMI, the two groups differed across multiple clinical characteristics beyond body mass, including age, race, sex and prevalence of diabetes, hypertension and hypercholesterolemia – all of which are associated with greater platelet activity, and at least in the case of diabetes, impaired responsiveness to aspirin [13]. In a subgroup in this study, the authors compared residual aggregation to 0.5 mM AA on 81 mg and 325 mg aspirin. They observed no additional reduction in platelet aggregation or urinary thromboxanes in either non-obese or obese subjects with the higher dose of aspirin – suggesting that higher doses of aspirin do not provide additional platelet COX1 inhibition in those of greater body weight.

A recent subject-level data meta-analysis from nearly 120,000 participants in primary prevention and secondary prevention of stroke trials showed that low-dose aspirin was ineffective at reducing major adverse cardiovascular events in those

![Figure 1. Platelet aggregation on exposure to 1.5 mM arachidonic acid (A & B) or 2 µM adenosine diphosphate (C & D) in the primary cohort before and after treatment with 81 mg aspirin for one week. Data are stratified by BMI and body weight categories. Graphs depict mean values ± upper and lower limits.

AA – arachidonic acid, ADP – adenosine diphosphate](image)

| BMI (kg/m²) | Platelet inhibition to AA (%) | Platelet inhibition to ADP (%) |
|------------|-------------------------------|-------------------------------|
| <25.0 (n = 54) | 80 [68, 90] | 31 [17, 42] |
| 25.0-29.9 (n = 24) | 87 [66, 92] | 29 [24, 40] |
| ≥30.0 (n = 6) | 95 [77, 98] | 43 [9, 63] |
| P-value | 0.18 | 0.73 |
| Body weight (kg) | | |
| <70 (n = 40) | 82 [68, 90] | 29 [19, 41] |
| 70–90 (n = 37) | 85 [64, 91] | 32 [8, 43] |
| >90 (n = 7) | 91 [79, 95] | 38 [16, 62] |
| P-value | 0.58 | 0.63 |
weighing >70 kg. Incomplete platelet inhibition by low-dose aspirin in heavier subjects was suggested as a possible explanation. However, in silico modeling of data from a recent experimental study assessing serum TXB2 levels in 96 subjects across a wide range of BMI (<20 to >40 kg/m²) showed that body weights of up to approximately 100 kg and BMI up to 35 kg/m² are compatible with complete COX1 inhibition by low-dose aspirin [19]. Additionally, a recent analysis of the influence of body weight and BMI/obesity status on platelet activity found elevated platelet surface P-selectin in obese patients [20] (as we have also previously shown [21]) taking both low-dose aspirin (100 mg) and clopidogrel. However, consistent with this study, body weight correlated weakly ($r = -0.13$) with platelet aggregation measured by LTA (to 1.6 mM AA). Further, there was no difference in multiple measures of platelet aggregation and COX1 activity [20]. Given these and the present findings, alternative explanations for the results of the meta-analysis mentioned above [3] should be considered. Aspirin, even at low doses, is known to have other potential cardiovascular benefits beyond platelet inhibition. For example, aspirin also acetylates COX2 – an activity that allows for the synthesis of several aspirin-triggered specialized pro-resolving lipid mediators, such as 15 R-LXA4 [22]. These lipid species stimulate the active resolution of inflammation, and have substantial preclinical [23,24], and some clinical [25,26], evidence supporting their importance in mediating vascular inflammation resolution and improving vascular outcomes. Notably, COX1 inhibition occurs prior to hepatic metabolism of the drug, whereas COX2 acetylation depends upon systemic levels of acetylsalicylate, which are reduced in

Figure 2. Platelet aggregation on exposure to 0.5 mM arachidonic acid (A & B), 5 μM adenosine diphosphate (C & D), or 2 μg/mL collagen (E & F) in the validation cohort before and after treatment with 81 mg aspirin for four weeks and 325 mg aspirin for four weeks. Data are stratified by BMI and body weight categories. Graphs depict mean values ± upper and lower limits.

AA – arachidonic acid, ADP – adenosine diphosphate
obesity[27]. The influence of body weight/mass on synthesis of aspirin-triggered pro-resolving lipid mediators has not been investigated to date.

The relevance of body weight, mass and composition to pharmacokinetics, particularly of anti-platelet drugs, has been neglected, and recent statements have highlighted the need for research in this area[28]. In addition to the reports assessing the influence of obesity on the anti-platelet effects of aspirin discussed above, there are data that support a positive association between obesity and platelet aggregation and activation in subjects taking P2Y12 inhibitors including prasugrel [29] and clopidogrel [30–32]. However, they are often limited by concomitant aspirin use and/or a lack of off-treatment measures of platelet function. Furthermore, and in contrast to aspirin, a meta-analysis of multiple P2Y12 inhibitors found that their efficacy in reducing MACE was not influenced by BMI or body weight[33].

Limitations of our study include the modest number of total subjects and specifically of obese and severely obese subjects in the primary cohort. Furthermore, our subjects were healthy and young. The findings may not be the same in different populations, specifically individuals with obesity-associated comorbidities such as diabetes mellitus[13]. Additionally, we recognize that 1) we only performed a small number of many possible assessments of platelet function, 2) consistency of findings in regard to clinical factors influencing platelet activity across the myriad available tests is poor [34,35], and 3) response to anti-platelet therapy assessed by functional testing has not been shown to predict adverse clinical outcomes. Nonetheless, LTA remains the gold-standard method for clinically assessing platelet function and we noted a consistent absence of a detectable difference in effect to multiple agonists across two separate populations. Likewise, although the absence of complementary PGI-metabolite data is a further limitation, our analysis of TXB2 in both cohorts further supports the absence of an influence of body weight or mass on COX1-inhibition by aspirin.

In conclusion, our data do not support an effect of body weight or mass on the COX1-inhibition by low-dose aspirin in healthy individuals. Given the association of body weight with aspirin’s efficacy in the prevention of cardiovascular events[3], our observations suggest that other mechanisms may explain the reduced preventive efficacy of low-dose aspirin, relative to higher doses of aspirin, at weights >70 kg, which are present with higher dose aspirin. Further research into these mechanisms, as well as into optimal aspirin dosing in severely obese individuals, are warranted.

Disclosure statement
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Table III. Percent platelet inhibition by 81 mg and 325 mg aspirin on exposure to 0.5 mM arachidonic acid (AA), 2 µg/mL collagen, or 5 µM adenosine diphosphate (ADP) stratified by BMI and body weight categories in the validation cohort. Mean [Upper limit, lower limit].
Platelets aspirin body mass and weight

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