

CASE-CONTROL STUDY

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# Association between Low-Dose Aspirin Use and Increased Blood Lactate Concentrations: A Case-Control Study

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## Abstract

This study assesses the risk of severe hyperlactatemia (defined as lactate levels > 4 mmol/L) in patients undergoing chronic low-dose aspirin (ASP) therapy and estimates the strength of this association. A case-crossover design was employed, in which individuals who experienced the outcome also served as their own controls, with exposure evaluated during a pre-event period. Additionally, a person-day-based analytical approach was used to compare exposure between case and control periods. Among the case group (ASP exposed/unexposed), the distribution was 127/578, while in the control group it was 547/3,968, yielding an odds ratio (OR) of 1.6 (95% CI: 1.29–1.97;  $z = 4.31$ ;  $P < 0.0001$ ). The findings suggest a modest association between low-dose aspirin use (100 mg/day) and elevated lactate levels, particularly in its primary indication for secondary prevention of vascular ischemic events. Although the observed risk is relatively low (OR = 1.6), clinical monitoring is advisable, especially when aspirin is co-administered with agents sharing similar toxicological profiles. Incorporating lactate level assessment into therapeutic management plans may enhance patient safety and therapeutic outcomes.

**Keywords** Aspirin, Lactate, Case-control study, Vascular ischemic event

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## Introduction

Lactic acid is a natural byproduct of normal metabolic activity. However, elevated lactate levels are frequently observed in pathological conditions and can result in significant alterations in circulatory dynamics. As such, hyperlactatemia is not only a potential marker of clinical deterioration but also a possible therapeutic target. Both the degree of lactate elevation and the duration required for normalization are strongly associated with mortality risk [1–3].

Under normal conditions, serum lactate levels remain below 2 mmol/L. Hyperlactatemia is defined as a concentration between 2 and 4 mmol/L, while severe hyperlactatemia is defined as a concentration exceeding 4 mmol/L. When accompanied by a blood pH  $\leq 7.35$  and PaCO<sub>2</sub>  $\leq 42$  mmHg, it may progress to lactic acidosis [4].

It is essential to recognize that elevated blood lactate levels can occur even with adequate tissue oxygenation. Nevertheless, lactic acidosis commonly develops due to inadequate tissue perfusion, metabolic disturbances, or the influence of pharmacological agents [4]. Lactic acidosis is generally classified into two types: Type A, associated with tissue hypoxia and hypoperfusion, and Type B, which occurs independently of oxygen delivery. Both forms reflect a common pathophysiological mechanism: mitochondrial dysfunction in the processing of pyruvate.

Type B lactic acidosis includes drug-induced cases [4]. Various pharmacological agents, including ethanol, acetaminophen, antiretrovirals,  $\beta$ -adrenergic agonists, biguanides (e.g., metformin), cocaine, cyanide, halothane, propofol, isoniazid, salicylates, valproic acid, and sulfasalazine, are known contributors to this condition. However, the available data on drug-induced hyperlactatemia are limited, primarily deriving from small-scale retrospective or prospective investigations. One of the few comprehensive studies was conducted by Jung *et al.* as a multicenter prospective analysis [5].

Among drugs implicated in mitochondrial toxicity, aspirin (ASP) has been reported to impair oxidative phosphorylation by depleting coenzyme Q10 (CoQ10) [6–8]. This mechanism may lead to hyperlactatemia and, in some cases, lactic acidosis. Studies have shown that aspirin can significantly lower serum CoQ10 levels, with lactic acidosis reported as a rare but serious complication [9]. Furthermore, elevated lactate levels may appear without any apparent underlying pathology in specific individuals, necessitating consideration of drug-induced origins.

In this context, the present study aims to assess the risk of severe hyperlactatemia (lactate > 4 mmol/L) and, in select cases, lactic acidosis (lactate > 5 mmol/L) in patients receiving long-term low-dose aspirin therapy, where the cumulative pharmacologic effect may play a significant role.

## Materials and Methods

This investigation used a case-crossover design, in which each subject who experienced the outcome of interest also contributed data for their own control period. Specifically, the *case period* refers to the time frame during which the outcome occurred, while the *control period* is a prior interval without the outcome, allowing for within-subject comparison [10].

To enhance temporal resolution, the analysis was also conducted using a person-day model, which measures exposure risk based on the number of days each participant was under observation rather than by individual-level data. This method estimates cumulative risk time across all participants, with individuals contributing person-days to both the control and case datasets, depending on whether the outcome is present or absent [11, 12].

The study aimed to quantify the association between long-term low-dose aspirin use and the incidence of elevated lactate levels above 4 mmol/L. The sample included all patients admitted to the Internal Medicine department of a small general hospital (fewer than 200 beds) during 2022 and 2023. Patients were excluded if they were receiving medications or had medical conditions known to influence lactate levels, such as metformin, statins, propofol, valproic acid, salbutamol, linezolid, epinephrine, nitroprusside, or if they were diagnosed with conditions like cirrhosis, cancer, kidney or respiratory failure, alcoholism, or AIDS.

The key variable was the accumulated number of person-days for each drug administered throughout the study. Cases were defined as person-days with lactate concentrations exceeding 4 mmol/L, while controls were defined as person-days with lactate concentrations at or below this level. The proportion of exposure to aspirin in both groups was then compared, and an odds ratio (OR) was calculated to estimate the strength of association.

Data were extracted from the hospital's laboratory database and electronic prescribing systems. Statistical significance was assessed using the chi-square test, and to correct for multiple comparisons across 28 medications, a Bonferroni-adjusted threshold was applied ( $P < 0.0017$ ).

## Results and Discussion

A total of 537 patients were enrolled in the study. The cohort had a mean age of 87 years ( $\pm 6$ ), a body mass index of 31.3 ( $\pm 2.9$ ) kg/m<sup>2</sup>, an average height of 159 cm ( $\pm 12$ ), and a mean weight of 81 kg ( $\pm 18$ ). Females comprised 47% of the

sample. All participants were polymedicated (taking five or more drugs), were prescribed 100 mg of aspirin daily, and were admitted to the internal medicine unit of a small hospital with fewer than 200 beds, where they remained hospitalized for an average of 7.5 days. The mean lactate level among cases was  $4.9 \pm 1.0$  mmol/L, compared to  $2.1 \pm 0.3$  mmol/L in controls.

The cumulative number of person-days (PDs) analyzed was 5,220, with 705 PDs corresponding to cases (lactate > 4 mmol/L) and 4,515 to controls (lactate  $\leq 4$  mmol/L). Among cases, 127 PDs were associated with aspirin exposure, while 578 were not. In the control group, 547 PDs were exposed to aspirin, and 3,968 were not. This yielded an odds ratio (OR) of 1.59 (95% CI: 1.29–1.97;  $z = 4.31$ ;  $P < 0.0001$ ).

Although the association between low-dose aspirin use and elevated lactate levels was statistically significant, its magnitude was modest. According to Cohen's criteria, an OR less than 2 suggests a weak effect size. However, this relationship becomes more clinically relevant when considering aspirin's routine use alongside other agents with similar mitochondrial toxicity, potentially amplifying the risk of hyperlactatemia and, in specific scenarios, progressing to lactic acidosis.

It is important to note that lactic acidosis does not always lead to acidemia. The development of acid-base disturbances depends on the extent of lactate accumulation, the body's buffering capacity, and coexisting physiological conditions such as compensatory hyperventilation or metabolic alkalosis, which may arise in settings like liver dysfunction or sepsis. Thus, elevated lactate may be observed alongside acidic, neutral, or even alkaline blood pH values [13].

Cohen and Woods previously classified lactic acidosis into two main categories: type A, related to tissue hypoxia, and type B, which is unrelated to oxygen delivery. Within type B, subtype B2 includes cases explicitly drug- or toxin-induced, involving agents such as biguanides, ethanol, iron, isoniazid, zidovudine, and salicylates [14, 15].

Aspirin, a widely accessible over-the-counter drug valued for its analgesic, anti-inflammatory, and antipyretic properties, can become hazardous when misused or overdosed—intentionally or inadvertently. Its mechanism of toxicity involves disruption of mitochondrial pyruvate metabolism, leading to lactate accumulation and potentially lactic acidosis [16].

Management of such drug-induced cases typically involves discontinuing the offending agent. Delay in recognition or withdrawal of the causative drug is often linked to unfavorable outcomes.

It should be emphasized that studies relying on secondary data sources, as in this case, provide valuable insights into routine clinical settings. However, such designs are inherently observational and are best suited for hypothesis generation rather than definitive causal inference.

## Conclusion

The use of low-dose aspirin (100 mg), primarily indicated for secondary prevention of vascular ischemic events, was associated with a modest increase in the risk of lactatemia exceeding 4 mmol/L (OR = 1.6), suggesting a weak but statistically significant association. Despite the low magnitude of risk, clinical vigilance is warranted, particularly when aspirin is administered alongside other agents known to impair mitochondrial function. Incorporating routine lactate monitoring into therapeutic protocols may enhance patient safety and support early identification of drug-induced metabolic disturbances.

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## Conflict of interest

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## Ethics statement

None

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