



# An Unexpected Cause of Hepatotoxicity and Myopathy in A Patient with Coronary Artery Disease: It Is Not Statin

Gamze Babür Güler<sup>1</sup>, Ekrem Güler<sup>1</sup>, Gültekin Günhan Demir<sup>1</sup>, Hacı Murat Güneş<sup>1</sup>, Zeynep Işıl Uğurad<sup>2</sup>, Öykü Önal Musallar<sup>3</sup>

<sup>1</sup> University of İstanbul Medipol, Faculty of Medicine, Department of Cardiology, İstanbul, Turkey

<sup>2</sup> İstinye State Hospital, Clinic of Psychiatry, İstanbul, Turkey

<sup>3</sup> University of İstanbul Medipol, Faculty of Medicine, Department of Psychiatry, İstanbul, Turkey

## ABSTRACT

Sertraline is a selective serotonin reuptake inhibitor; it is safe and effective for treating depression in patients with coronary artery disease. Although nausea, diarrhea, and dyspepsia are common adverse effects, less frequent reactions such as maculopathy, hepatotoxicity, and rhabdomyolysis have also been reported. In patients receiving multiple drugs for co-morbid conditions (heart failure, coronary artery disease, etc.), these side effects can be underdiagnosed. Here, we present a patient with coronary artery disease and elevated liver function tests and skeletal muscle enzymes who had multiple admissions and prolonged follow-ups in the emergency room because of elevated creatine kinase and creatine kinase-MB levels, which delayed his appropriate management including discontinuation of sertraline instead of statin.

**Key Words:** Coronary artery disease; hepatotoxicity; myopathy; sertraline

## Koroner Arter Hastalığı Olan Bir Hastada Beklenmedik Bir Hepatotoksisite ve Miyopati Nedeni: Statin Değil

### ÖZET

Sertralin koroner arter hastalığına eşlik eden depresyon durumlarında etkinliğini ve güvenilirliğini kanıtlamış bir selektif serotonin geri alım inhibitörüdür. Sık görülen yan etkileri yanında (bulantı, ishal, dispepsi) daha nadir görülen (makülopati, hepatotoksisite, rabdomyoliz) gibi yan etkileri de bildirilmiştir. Çoklu ilaç kullanımının sık olduğu hastalarda (kalp yetersizliği, koroner arter hastalığı gibi) depresyon tedavisinde sertralin kullanımına bağlı yan etkiler gözden kaçabilmektedir. Biz karaciğer fonksiyon testleri ve kas enzimleri yükselemiş bir koroner arter hastasında sertralinin; statinlerden sonra etyolojik ajan olarak değerlendirildiği ve bu sürede kreatinin kinaz, kreatinin kinaz-MB yüksekliği nedeniyle uzamış acil servis takipleri olan bir olguyu sunuyoruz.

**Anahtar Kelimeler:** Koroner arter hastalığı; hepatotoksisite; miyopati, sertralin

## CASE REPORT

A 46-year-old male patient with complaints of chest pain and fatigue was admitted to our outpatient clinic. His medical history was unremarkable except for primary stenting in the right coronary artery for inferior myocardial infarction in January 2014. He was prescribed clopidogrel (75 mg), metoprolol (50 mg), ramipril (5 mg), acetylsalicylic acid (100 mg), and atorvastatin (20 mg) therapy. The patient suffered symptoms related to anxiety disorders (fear of death, sense of refractory chest pain, and multiple hospital admissions) after acute coronary syndrome (ACS); thus, control angiography had been performed, which revealed stent patency. A consultant psychiatrist prescribed sertraline (50 mg once a day), which was later increased to 100 mg once a day. Although most of his symptoms related to anxiety disorder had improved significantly with sertraline treatment, his visits to the emergency room for chest pain persisted. Detection of elevated creatine kinase (CK) and creatine kinase-MB (CK-MB) levels at his multiple visits led to prolonged and repeated cardiac troponin follow-ups, which were all negative. Prolonged ER follow-ups for serial testing gave rise to increased anxiety. Meanwhile, his fatigue persisted. On admission to our clinic, his laboratory findings were as follows: CK [733.2 U/L (range, 24-170 U/L)], lactate dehydrogenase [LDH; 546 U/L (range, 225-450 U/L)], aspartate aminotransferase [AST; 93.6 U/L (range, 0-35 U/L)], alanine transaminase [ALT; 168.1 U/L (range, 0-45 U/L)], gamma-glutamyltranspeptidase

## Correspondence

Gamze Babür Güler

E-mail: gamzebabur@hotmail.com

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[GGT; 63.6 U/L (range, 0-55 U/L)]. His medical history did not include any abnormalities (history of hepatitis, active infection, or vigorous exercise) potentially associated with those high levels. Thereafter, his statin dose decreased by half-dose. A follow-up visit six weeks later revealed insignificant decreases in laboratory tested levels as follows: CK [720 U/L (U/L 0-200 U/L)], CK-MB [32 U/L (range, 0-25 U/L)], AST [50 U/L (range, 0-40 U/L)], ALT [77 U/L (range, 0-50 U/L)], LDH [356 U/L (range, 0-225 U/L)], GGT [51 U/L (range, 0-61 U/L)]; thus, liver ultrasound exam, serological markers for hepatitis, prothrombin time, and bilirubin tests were evaluated, and no abnormality was detected. The patient was subsequently consulted with psychiatry, and sertraline was replaced with a selective serotonin reuptake inhibitor (SSRI) excreted via the kidney. His liver tests performed eight weeks later were within the normal ranges: AST [40 U/L (range, 0-40 U/L)], ALT [0-31 U/L (range, 7-49 U/L)], GGT [26 U/L (range, 10-71 U/L)], as well as his CK [174 U/L (range, 20-190 U/L)] and CK-MB [0-30 U/L (range, 0-25 U/L)] levels. Statin therapy was re-initiated, and his liver function tests were not elevated.

## DISCUSSION

SSRIs are widely prescribed agents for treatment of depression caused by cardiovascular side effects (tachycardia and orthostatic hypotension) less common than old-generation tricyclic antidepressants<sup>(1)</sup>. Sertraline, a popular member of this group, was shown to be safe and effective for treating depression in patients with heart disease<sup>(2)</sup>. SADHART (Sertraline antidepressant heart attack randomized trial) compared sertraline and placebo in patients diagnosed with depression within 30 days after ACS and demonstrated that sertraline was a safe and well-tolerated agent<sup>(3)</sup>. Although growing numbers of evidence confirmed the safety of sertraline, the number and variety of reported adverse effects continue to increase. In this report, we aimed to show that sertraline therapy induced hepatotoxicity and myositis in a patient with coronary artery disease whose appropriate diagnosis and treatment were delayed because of concurrent statin therapy.

Multi-drug use is common in patients with heart diseases because of comorbidities; thus, concerns for drug interaction and safety ensue in this patient population. In an *in vitro* study, it was demonstrated that sertraline is metabolized as cytochrome isoforms by multiple enzymes<sup>(4)</sup>. Sertraline has mild effects on inhibition of CYP isoenzymes; thus, it is associated with uncommon drug-drug interactions<sup>(5)</sup>. To our knowledge, there is no data about the additive effect of sertraline and statin use with regard to liver and muscle toxicity. However, it is likely to occur when dominant hepatic metabolism for both these drugs are taken into account. In our patient, although statin therapy was interrupted, transaminase levels remained elevated with a mild decrease.

The most commonly observed adverse events associated with the use of sertraline were nausea, diarrhea/loose stools

and dyspepsia, male sexual dysfunction (mainly delayed ejaculation), insomnia and somnolence, tremor, increased sweating and dry mouth, and dizziness in product information<sup>(6)</sup>. Incidence of asymptomatic increases in serum transaminases with sertraline use was 0.5%; meanwhile, acute fatal hepatitis related to sertraline use had been reported in literature<sup>(7)</sup>. Hepatotoxic effects of sertraline comprise complex mechanisms; however, the most attributed ones include apoptosis induced by prolonged endoplasmic reticulum stress and apoptosis mediated by mitogen-activated protein kinase signaling pathways<sup>(8,9)</sup>. It is not surprising to see hepatotoxic effects of a drug that is highly metabolized by the liver; however, the underlying mechanism for skeletal muscle injury remains yet to be elucidated. Rhabdomyolysis in a 71-year-old patient with dementia was claimed to be induced by vasoconstriction/vasospasm associated with sertraline and comorbidities as an underlying cause of muscle ischemia<sup>(10)</sup>.

## CONCLUSION

Mechanisms for liver and muscle toxicity associated with sertraline use continue to be unclear. When considering the co-existence of coronary artery disease and psychiatric disorders, it would be wise to emphasize that a combination of statin and sertraline seems to be an issue, which both cardiologists and psychiatrists need to be cautious about. We suggest keeping in mind the risk of hepatotoxicity and myositis associated with sertraline use in this specific but common patient population.

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