

## Invited Editorial / Davetli Editöryal Yorum

### Obesity, leptin, and thrombosis: Focus on clopidogrel resistance

#### Obezite, leptin ve tromboz: Klopidoğrel direncine bakış

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Leptin is an adipocyte-derived hormone (adipokine) that acts as a key factor for maintenance of energy homeostasis. In most obese individuals, serum leptin levels are increased and correlate with individual's body mass index.<sup>[1]</sup> The role of leptin in regulating blood pressure, activating sympathetic nervous system, insulin resistance, angiogenesis, inflammatory vascular responses, platelet aggregation, and arterial thrombosis suggests that leptin may be closely related to development of cardiovascular events.<sup>[2]</sup> Several clinical studies have also shown that obesity and hyperleptinemia are associated with cardiovascular diseases such as hypertension, diabetes, atherosclerosis, and coronary heart disease.<sup>[3]</sup> Therefore, leptin is considered an important link between obesity and cardiovascular disease.

Obesity increases propensity for thrombosis, and this tendency for thrombosis is suggested to be related to a variety of mechanisms, including the actions of adipocyte-derived hormones such as leptin.<sup>[4]</sup> Hyperleptinemia carries an increased risk for thrombotic events such as ischemic stroke and acute myocardial infarction, independent of other risk factors.<sup>[5]</sup> In the context of the association between obesity and thrombosis, leptin has been one of the most extensively studied adipokines. The leptin receptor (L-receptor) has been detected on platelets, and leptin appears to exert direct prothrombotic effects through these receptors.<sup>[6]</sup> Leptin induces platelet aggregation by potentiating response to platelet agonist adenosine

diphosphate (ADP).

<sup>[7]</sup> ADP is a weak but important agonist

that only directly in-

duces a shape change and reversible platelet aggregation, whereas the ensuring secretion and secondary aggregation are caused by ADP-induced synthesis of thromboxane A2. ADP plays an essential role in platelet function, since it amplifies responses induced by other agonists after secretion from platelet-dense granules and this mechanism is known to be enhanced by leptin.<sup>[8]</sup> In vivo studies have shown that leptin-deficient mice were characterized by prolonged time to thrombotic vascular occlusion despite presence of obesity and related metabolic abnormalities; however, when recombinant leptin was injected, it significantly enhanced arterial thrombus formation in both leptin-deficient and wild type mice.<sup>[9]</sup> Further studies supported this finding demonstrating that neutralizing leptin antibody inhibits prothrombotic effects of endogenous leptin.<sup>[10]</sup> Clinical studies have also shown that platelets from obese patients were leptin-sensitive and had enhanced ADP-induced aggregation in comparison to platelets from lean patients. A more interesting observation is that high concentrations of leptin corresponding to levels in obese individuals increased platelet aggregation, whereas lower concentrations did not. This finding suggests that prothrombotic effect of leptin might be limited to obese hyperleptinemic individuals.<sup>[11]</sup>

#### Abbreviations:

ADP Adenosine diphosphate

PCI Percutaneous coronary interventions

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Thienopyridines such as clopidogrel lead to inhibition of platelet activity through inhibition of ADP P2Y<sub>12</sub> receptor. In the present issue of Archives of the Turkish Society of Cardiology, Doğan et al. have published a study investigating whether high serum leptin levels contributed to clopidogrel resistance in obese patients undergoing percutaneous coronary interventions (PCI).<sup>[12]</sup> Present data suggest that leptin leads to ADP-induced platelet aggregation; therefore, hypothetically, high leptin levels in obese patients may attenuate the effect of clopidogrel and cause clopidogrel resistance. Previous studies have shown lower sensitivity to clopidogrel in obese patients; however, etiology underlying this finding is ambiguous. Doğan et al. divided 100 coronary artery patients undergoing PCI into 2 groups based on presence or absence of clopidogrel resistance, and association of serum leptin levels with clopidogrel resistance was investigated. The authors found that clopidogrel resistance was more prominent in patients with hyperleptinemia (leptin $\geq$ 15 ng/mL). While statistically significant, small number of hyperleptinemic patients (n=11) and overall study population (n=100) prominently diminishes the power of this study. Leptin circulates in the blood at level of 5 to 15 ng/mL and this level may reach up to 50 ng/mL in obese individuals.<sup>[13]</sup> However, aggregation of human platelets is enhanced only by very high concentrations of leptin (100–500 ng/mL) *in vitro*. Therefore, it would be informative to provide mean leptin value of hyperleptinemic patients. Higher cut-off leptin level could be set for future studies in order to increase the power of the study. Finally, contrary to common perception, a number of studies have suggested that leptin may have some protective effects on cardiovascular system. Some authors also argue that obese individuals are resistant to leptin, and therefore, leptin-associated harm is due to leptins inability to elicit its effects appropriately.<sup>[13]</sup>

In conclusion, both obesity and high leptin levels seem to increase propensity for thrombosis, and leptin leads to ADP-induced platelet activation, which may blunt effect of clopidogrel on thrombocytes. Therefore, more potent antiplatelet agents such as ticagrelor and prasugrel could be considered for obese and

hyperleptinemic patients with higher thrombotic risk.

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