Paladino, Francesco Del Sole, Marta Novo, Vittoria Cammisotto, Paola Andreozzi, Maria Santulli, Fortunata Vasaturo, Tiziana Di Stefano, Patrizia Iannucci, and Elio Sabbatini.

#### REFERENCES

- 1. Pastori D, Nocella C, Farcomeni A, et al. Relationship of PCSK9 and urinary thromboxane excretion to cardiovascular events in patients with atrial fibrillation. J Am Coll Cardiol 2017;70:1455–62.
- 2. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA 2016;316:2373-84.
- **3.** Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
- **4.** Violi F, Loffredo L, Carnevale R, Pignatelli P, Pastori D. Atherothrombosis and oxidative stress: mechanisms and management in elderly. Antioxid Redox Signal 2017;27:1083–124.
- **5.** Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376: 1713-22.

# Breakfast Skipping, Atherosclerosis Disease, and Free Fatty Acids



I read with great interest the study by Uzhova et al. (1) and found the odds ratios for atherosclerosis associated with breakfast pattern especially impressive. Those who skip breakfast (breakfast skippers) are at greater risk than those who take a low-energy breakfast (LEB), whereas those who take a high-energy breakfast have the lowest risk.

The challenge is to understand these results in the light of physiology. It is known that after overnight fast, free fatty acids (FFAs), a primary source of energy, are increased in the morning. Additionally, sleep restriction relative to normal sleep results in increased FFA levels during the early morning hours. This may be counteracted by a morning high-carbohydrate meal, which can lower the level of blood FFAs, as it is known that insulin inhibits lipolysis. However, even among those who do not skip breakfast, FFA levels peak in the morning (2).

Coincidently, myocardial infarction and sudden cardiac death also peak in the morning (3). This relationship is explained in my 2017 study (4). The physiological mechanism is described in my 2016 study (5): FFAs together with (even mild) states of acidemia (blood pH level of <7.35) shape the context for formation of fatty acid micelles and vesicles with an acidic core, which fuse with endothelia, create inflammation, and thereby may initiate atherosclerotic plaque formation. At the sites of vesicle attachment, release of the acidic core creates

an acidic spot. Calcification occurs in the presence of free calcium that is released from circulating albumin due to loss of affinity to calcium as blood pH drops below normal levels.

The preceding physiological mechanism also explains why LEB poses a lower risk than skipping breakfast. In fact, LEB reduces the level of FFAs by only a small amount, thus only slightly alleviating the critical conditions for the formation of FFA vesicles.

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### REFERENCES

- 1. Uzhova I, Fuster V, Fernández-Ortiz A, et al. The importance of breakfast in atherosclerosis disease. J Am Coll Cardiol 2017;70:1833-42.
- **2.** Portaluppi F, Lemmer B. Chronobiology and chronotherapy of ischemic heart disease. Adv Drug Deliv Rev 2007;59:952-65.
- **3.** Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987;75:131–8.
- **4.** Reis AH. Acidemia and blood free fatty acids: analysis of cardiovascular risk factors in a new context. Discov Med 2017;23:183-8.
- **5.** Reis AH. On the etiology of cardiovascular diseases: a new framework for understanding literature results. Med Hypotheses 2016;92:94–9.

## Is Skipping Breakfast a Marker for Current Smoking?



Recent publications from the PESA (Progression of Early Subclinical Atherosclerosis) (1,2) supporting associations between skipping breakfast, social eating, and prevalence of subclinical atherosclerosis and from the Japan Public Health Center-based study (3) of clinical stroke are evocative and require additional analyses in other populations. These studies, which are difficult to accomplish, may require statistical manipulations to adjust for the many differences among the observations being analyzed. These statistical manipulations may mask other important observations. The studies in Spain and Japan have higher prevalence of smoking than those reported in the U.S. Health Professionals Study (4). In each of