Circulating free fatty acids (FFAs) are elevated in metabolic syndrome and hypertension and may cause the impairment of endothelial function and are associated with cardiovascular risk factors linked to insulin resistance including hypertension. Endothelium maintains NO production and preserves vascular protection as consequence of vascular relaxation, inhibition of platelet aggregation and adhesion and inhibition of leukocyte adhesion. High FFAs levels contribute to hypertension and cardiovascular disease by impairing NO-dependent relaxation. In this study, we evaluated the effect of oleic and linoleic acids on NO release by endothelial cells in presence of olive oil minor compounds such as tyrosol and sitosterol. These findings are compared with the changes of NO serum levels and blood pressure after 12-month follow-up virgin olive oil (rich in oleic acid and minor compounds) or nuts (rich in linoleic acid) intervention in aged nonsmoking women at high cardiovascular risk recruited into the large-scale trial PREDIMED. Results showed that hypertensive patients had low serum NO levels and that olive oil intervention significantly enhanced NO serum levels while reduced blood pressure. Oleic acid (0-100 μmol/L) reduced NO release by ECV304 cells. This effect was more marked with linoleic acid (0-100 μmol/L). Interestingly, the presence of tyrosol (10-30 μM) and sitosterol (10-30 μM) or both (30 μM) reverted the impairment of NO concentrations induced by oleic acid and reached NO levels higher than control condition. These findings that can be related with the increase of sera NO levels as well as the reduction of blood pressure in patients that consumed olive oil diet.