Background: Increased oxidative stress or an impaired antioxidant defense mechanism may play a crucial role in the onset and progression of atherosclerosis. Paraoxonase-1 (PON1) which accounts for most of the antioxidant effect of high density lipoprotein cholesterol has been presented as a potential therapeutic agent against atherosclerosis development. Alleles frequency of PON1 gene that influence enzyme concentration as well as activity differs greatly among ethnic groups and data from several studies showed ethnic variations in the interpretation of cardiovascular disease (CVD) associated with PON1 polymorphisms. Objectives: To investigate PON1 Q192R and L55M polymorphisms in Egyptian patients with type 2 diabetes mellitus (T2DM) and its association with CVD. Methods: This study included 184 subjects classified into 3 groups; T2DM, T2DM with CVD, and healthy controls. PON1 polymorphisms were genotyped by real-time PCR and PON1 concentration was assayed in serum by ELISA (enzyme linked immunesorbent assay). Results: PON1-192R and -55L alleles were association with T2DM (p=0.02 and 0.009, respectively). Q192R polymorphism was associated with CVD in our diabetic patients (p=0.01). Serum PON1 concentration was significantly reduced in diabetic patients compared to controls and lowest enzyme concentrations were associated with 192R allele (p=0.04). Multiple logistic regression analysis revealed significant correlations between 192R allele and other independent CVD risk factors. Conclusion: Our results showed that PON1 192R and 55L alleles are associated with T2DM and suggest that they may play a role in the pathogenesis of the disease. Q192R might represent a novel risk factor for CVD in Egyptian patients with T2DM.