

## **Obesity and Inflammation: associated polymorphisms**

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### **Abstract**

Objective: Obesity has been characterized by a state of chronic low-grade inflammation, given that increased levels of the inflammatory markers have been related with adiposity. The assumption is that adipokines, cytokines, and other factors produced and released by fat are responsible for the chronic inflammatory state of obesity. Once that IL-6, IL-1 and TNF are increased in adipocytes in the obese state and are early-acting inducers of inflammatory cascades, genetically determined subsets of the population may have altered acute phase responses to certain stimuli. Therefore, we studied the influence of fat distribution in the inflammatory outcome phenotype of specific polymorphisms affecting genes encoding pro-inflammatory cytokines.

Design: Cross-sectional study.

Subjects: 411 non-institutionalized inhabitants of Porto, Portugal.

Measurements: Participants answered a structured questionnaire and were genotyped for the following polymorphisms: IL-6 -174 G/C, IL1 $\beta$  -511C/T, TNF $\alpha$  -308G/A.

Analytical and anthropometrics measurements were obtained after 12 h fasting. CRP, fibrinogen, leukocytes and uric acid levels were measured.

Results: Genotyping of the IL-6 -174 G/C polymorphism was performed in 322 people. There were 144 (44.7%) participants with GG genotype, 132 (41.0%) GC heterozygotes, and 46 (14.3%) CC homozygotes. It was found a significant association between waist circumference and C carriers – GC ( $\beta=0.039$ ,  $p<0.001$ ) and CC

( $\beta=0.037$ ,  $p=0.006$ ), within C-reactive protein. No interaction was found between waist circumference and C carriers, in relation to leukocytes, but this association became statistically significant after adjustment for gender, age and smoking habits when comparing GG homozygotes with heterozygotes GC ( $\beta=0.022$ ,  $p=0.018$ ) and with homozygotes CC ( $\beta=0.045$ ,  $p=0.020$ ). There is a significant association between waist circumference and C carriers in relation to uric acid levels – GC ( $\beta=0.392$ ,  $p<0.001$ ) and CC ( $\beta=0.485$ ,  $p=0.007$ ). In relation to fibrinogen, it was found a significant association between waist circumference and homozygotes GG ( $\beta=-0.002$ ,  $p=0.015$ ) and GC genotype ( $\beta=0.016$ ,  $p=0.006$ ).

Genotyping of the IL1 $\beta$  -511 C/T polymorphism was performed in 254 subjects. There were 110(43.3%) participants with CC genotype, 106(41.7%) heterozygotes CT, and 38(15.0%) homozygotes TT. It was found no interaction between waist circumference and homozygotes TT, in relation to CRP concentrations. The interaction of homozygotes CC ( $\beta=0.027$ ,  $p<0.001$ ) and heterozygotes CT ( $\beta= -0.027$ ,  $p<0.001$ ) with WC showed an effect on CRP concentrations, even after adjustment for gender, age and smoking habits. In relation to leukocytes, there is no interaction between waist circumference and C carriers, but once adjusted for gender, age and smoking habits, the interaction between waist circumference and CC homozygotes ( $\beta=0.028$ ,  $p=0.009$ ) and heterozygotes CT ( $\beta= -0.026$ ,  $p=0.018$ ) affected leukocyte levels. No interaction was seen between waist circumference and homozygotes TT, in relation to uric acid concentrations. The interaction of homozygotes CC ( $\beta=0.586$ ,  $p<0.001$ ) and heterozygotes CT ( $\beta= -0.543$ ,  $p<0.001$ ) with WC showed an effect on uric acid levels, even after adjustment for gender, age and smoking habits. The interaction of homozygotes CC ( $\beta=0.016$ ,  $p=0.038$ ) and heterozygotes CT ( $\beta=-0.018$ ,  $p=0.021$ ) with WC showed an effect on fibrinogen concentrations, and no interaction was found between waist circumference and homozygotes TT.

Genotyping of the TNF- $\alpha$  -308 G/A polymorphism was performed in 308 subjects. There were 228(74.0%) participants with GG genotype, 76(24.7%) heterozygotes GA,

and 4(1.3%) homozygotes AA. It was found no interaction between waist circumference and homozygotes GG and AA, in relation to CRP concentrations. The interaction of heterozygotes GA with WC showed an effect on CRP concentrations ( $\beta=0.038$ ,  $p<0.001$ ), even after adjustment for gender, age and smoking habits. There is also no interaction between waist circumference and GG, GA and AA genotypes, in relation to leukocytes concentrations. The interaction of GG and GA genotypes with WC showed an effect on uric acid concentrations ( $\beta=0.056$ ,  $p<0.001$  and  $\beta=0.410$ ,  $p=0.003$ , respectively), even after adjustment for gender, age and smoking habits. It was found no interaction between waist circumference and genotypes GG, GA and AA, in relation to fibrinogen concentrations. After adjustment for gender, age and smoking habits, the interaction of homozygotes GG ( $\beta=-0.002$ ,  $p=0.034$ ) and heterozygotes GA ( $\beta=-0.017$ ,  $p=0.001$ ) with WC showed an effect on fibrinogen concentrations.

Conclusions: For the analysed polymorphisms, there is an interaction with waist circumference in relation to at least one inflammatory marker level.