

# The development of diabetes in obese subjects : the interaction of p53 codon 72 and ACP<sub>1</sub>

Gloria-Bottini F<sup>1\*</sup>, Banci M<sup>2</sup>, Neri A<sup>1</sup>, Magrini A<sup>1</sup> and Bottini E<sup>1</sup>

<sup>1</sup>Department of Biomedicine and Prevention, University of Rome Tor Vergata, School of Medicine, Rome, Italy

<sup>2</sup>Valmontone Hospital, Rome, Italy

## Abstract

Previous studies have shown that the relationship between obesity and diabetes is influenced by the genotypes of ACP<sub>1</sub> and p53 codon 72. In particular the \*B/\*B genotype of ACP<sub>1</sub> and carriers of \*Pro allele of p53 codon 72 show a low odds ratio for diabetes in obese subjects.

In the present paper we have searched for a possible interaction between the two polymorphisms concerning their effects on the relationship between obesity and diabetes.

Two hundred and eighty two subjects admitted to the hospital for cardiovascular diseases were studied in the population of Rome. The genotypes of ACP<sub>1</sub> and p53 codon 72 were determined by DNA analysis.

The data suggest an additive effect of the two genetic systems concerning the relationship between obesity and diabetes: The maximum O.R. for diabetes in obese subjects is observed in those carrying no protective factors (\*B/\*B and \*Pro allele) while the minimum O.R. is observed in subjects carrying both factors. The study of these genotypes in obese subjects may have relevance to prevent clinical manifestations of diabetes.

## Introduction

Previous study has shown that the susceptibility to type 2 diabetes (T2D) in obese subjects depends on the genotype of p53 codon 72 and it is higher in \*Arg/\*Arg subjects than in those carrying the \*Pro allele [1]. Another study has revealed that in subjects with ACP<sub>1</sub> \*B/\*B genotype the susceptibility to T2D in obese subjects is lower as compared to other ACP<sub>1</sub> genotypes [2].

We have now searched for possible interaction between the two genetic systems concerning their effects on the risk of T2D in obese subjects.

Acid Phosphatases locus 1 (ACP<sub>1</sub>) is a polymorphic enzyme showing different activities among genotypes. The enzyme is involved in glycide and lipid metabolism [3] and it has been found associated with obesity and diabetes [4,5]. The enzyme is composed of two isoforms that show different molecular and catalytic properties and different concentration among genotypes (Table 1). ACP<sub>1</sub> functions has phosphotyrosine phosphatase and flavin mononucleotide phosphatase. The enzyme is able to dephosphorylate a negative phosphorylation site in the ZAP 70 tyrosine kinase in T cells [6] leading to increased activation of this

kinase and enhanced signalling from T cell antigen receptors. ACP<sub>1</sub> is involved in the negative modulation of insulin signal transduction [7] and it is able to dephosphorylate the adipocyte lipid binding proteins (ALBP) in vitro [8]. In adipose tissue ALBP is phosphorylated on Tyr 19 after insulin stimulation and this phenomenon seems to impair its fatty acid binding ability [9]. Recently an important effect of the reduction of ACP<sub>1</sub> expression on insulin sensitivity has been observed in obese mice [10].

P53 codon 72 shows a single nucleotide substitution resulting in the presence of either arginine or proline in the aminoacid sequence : the arginine variant is a strong apoptosis inducer while the proline variant is a strong transcriptional activator [11]. A strong association of p53 codon 72 with T2D has been previously observed [12]. Moreover p53 expression in adipose tissue is involved in insulin resistance. The inhibition improves insulin resistance while upregulation of p53 activity leads to an increase to insulin resistance [13].

## Material and methods

Two hundred and eighty two subjects admitted to the hospital for cardiovascular disease were studied in the population of Rome: Informed Consent was obtained from all subjects to participate to the study that was approved by the Direction of the hospital. ACP<sub>1</sub>

**Table 1.** F and S isozyme concentrations in relation to the ACP1 genotype.

Total quantity of F (µg/ml RBC)		Total quantity of S (µg/ml RBC)	
*B/*B	16.4	*C/*C	20.6
*A/*B	12.0	*A/*C	12.7
*B/*C	11.3	*B/*C	12.1
*A/*A	7.9	*B/*B	3.9
*A/*C	7.5	*A/*B	3.4
*C/*C	5.7	*A/*A	3.3

The quantities of enzyme are given per ml of packed red cells.

**Correspondence to:** Fulvia Gloria-Bottini, Department of Biomedicine and Prevention, University of Tor Vergata, Via Montpellier,100133 Rome, Italy, Tel: +39 06 30889514; E-mail: gloria@med.uniroma2.it

**Key words:** diabetes; obesity; p53 codon 72; ACP<sub>1</sub>

**Received:** September 28, 2017; **Accepted:** November 14, 2017; **Published:** November 18, 2017

polymorphism was determined by DNA analysis as previously described [14]. P53 codon 72 genotype was determined by DNA analysis according to De La Calle Martin as previously described [15].

Three way contingency analysis was carried out by a log linear model according to Sokal and Rohlf [16]. Other statistical analyses were carried out by commercial software (SPSS).

## Results

Table 2 shows the effect of p53 codon 72 genotype on the relationship between ACP<sub>1</sub> and the development of diabetes in obese subjects. In \*Arg/\*Arg genotype the effect of obesity on the development of diabetes is much less strong in \*B/\*B genotype than in carriers of other ACP<sub>1</sub> genotypes. Such difference between \*B/\*B and other ACP<sub>1</sub> genotypes is much less evident in carriers of \*Pro allele.

Figure 1 shows the relationship between odds ratio for diabetes (obese versus non obese) and the number of protective factors (\*B/\*B genotype and \*Pro allele). The maximum odds ratio for diabetes is attained in absence of protective factors while the minimum odds ratio is observed in subjects carrying both factors.

In table 3 are reported the results of an analysis of the interaction among ACP<sub>1</sub>, diabetes and obesity in \*Arg/\*Arg genotype and in carriers of \*Pro allele. A three way contingency table analysis carried out by a log linear model has shown that in subjects with \*Arg/\*Arg genotype there is a borderline interaction among ACP<sub>1</sub>, diabetes and obesity and a strong additive effect of ACP<sub>1</sub> and obesity on diabetes. In subjects carrying the \*Pro allele there is no interaction and a borderline additive effect of ACP<sub>1</sub> and obesity for diabetes is observed.

## Discussion

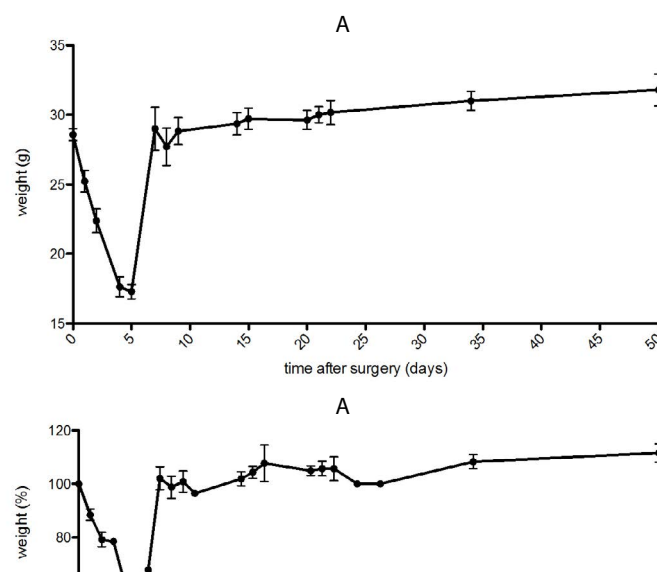
The present study has revealed a cooperative interaction between ACP<sub>1</sub> and p53 codon 72 concerning their effects on susceptibility to diabetes in obese subjects. \*B/\*B genotype of ACP<sub>1</sub> and \*Pro allele of p53 codon 72 are protective against development of diabetes in obese

**Table 2.** The effect of P53 codon 72 on the relationship between ACP<sub>1</sub> and the development of Type 2 diabetes in obese subjects.

	ACP <sub>1</sub> genotype			
	*B/*B		Other genotypes	
	Subjects with *Arg/*Arg genotype			
	% diabetes	Total n°	% diabetes	Total n*
BMI ≤30	20.8%	48	9.3%	75
BMI > 30	50.0%	14	65.0%	20
Chi-square	$\chi^2 = 3.283$ df=1 p=0.070		$\chi^2 = 26.184$ df= 1 p<10 <sup>-6</sup>	
O.R.	3.80		18.04	
95% C.I.	0.92-16.16		4.72-76.68	
	Subjects carrying the *Pro allele			
	*B/*B		Other genotypes	
	Subjects with *Arg/*Arg genotype			
	% diabetes	Total n°	% diabetes	Total n*
BMI ≤30	22.9%	48	14.3%	49
BMI > 30	45.5%	11	47.1%	17
Chi-square	$\chi^2 = 1.301$ df=1 p=0.254		$\chi^2 = 5.960$ df= 1 p=0.015	
O.R.	2.80		5.96	
95% C.I.	0.59-13.42		1.31-22.46	

**Table 3.** The effect of P53 codon 72 genotype on the interaction between ACP<sub>1</sub>, diabetes and obesity. Three way contingency table analysis by a log linear model.

	Interaction between ACP <sub>1</sub> , diabetes and obesity	Additive effect of ACP <sub>1</sub> and obesity on diabetes
*Arg/*Arg genotype	P=0.080	p≤0.0001
Carriers of *Pro allele (*Arg/*Pro and *Pro/*Pro)	P=0.500	P=0.030



**Figure 1.** The relationship between odds ratio for diabetes (obese vs non obese) and the number of protective factors (\*B/\*B genotype and \*Pro allele)

subjects: the minimum risk is observed in carriers of both factors while the maximum risk is observed in absence of these factors .

P53 expression in adipose tissue is involved in insulin resistance [13]; moreover an association of p53 codon 72 with T2D has been observed [12]. ACP<sub>1</sub> is able to dephosphorylate the Adipocide Lipid Binding Protein (ALBP) [8]. The coupled action of p53 and ACP<sub>1</sub> seems to influence the susceptibility of obese subjects to become diabetic. Further studies in this area would be rewarding.

From the practical point of view, the study of ACP<sub>1</sub> and p53 codon 72 polymorphisms could help to identify obese subjects at high risk to develop diabetes.

The limitation of the study is represented by the fact that it has been carried out in subjects with cardiovascular diseases.

## References

- Gloria-Bottini F, Banci M, Saccucci P, Magrini A, Bottini E (2011) Is there a role of p53 codon 72 polymorphism in the susceptibility to type 2 diabetes in overweight subjects? A study in patients with cardiovascular diseases. *Diabetes Res Clin Pract* 91: e64-67.
- Gloria Bottini F, Banci M, Saccucci P, Neri A, Pietrouisti A, et al. (2012) ACP<sub>1</sub> genetic variability and the development of diabetes in obese subjects. In *Type 2 diabetes: Causes, Treatment and Preventive Strategies*. Endocrinology Research and Clinical Development Metabolic Diseases-Laboratory and Clinical Research pp: 7-10.
- Bottini N, Bottini E, Gloria-Bottini F, Mustelin T (2002) Low-molecular-weight protein tyrosine phosphatase and human disease: in search of biochemical mechanisms. *Arch Immunol Ther Exp (Warsz)* 50: 95-104. [Crossref]
- Bottini E, Lucarini N, Gerlini G, Finocchi G, Sciré G, et al. (1990) Enzyme polymorphism and clinical variability of diseases: study of acid phosphatase locus 1 (ACP<sub>1</sub>) in obese subjects. *Hum Biol* 62: 403-411.
- Gloria-Bottini F, Gerlini G, Lucarini N, Borgiani P, Amante A, et al. (1996) Phosphotyrosine protein phosphatases and diabetic pregnancy: an association between low molecular weight acid phosphatase and degree of glycemic control. *Experientia* 52: 340-343. [Crossref]
- Bottini N, Stefanini L, Williams S, Alonso A, Jascur T, et al. (2002) Activation of ZAP-70 through specific dephosphorylation at the inhibitory Tyr-292 by the low molecular weight phosphotyrosine phosphatase (LMPTP). *J Biol Chem* 277: 24220-24224.
- Chiarugi P, Cirri P, Marra F, Raugei G, Camici G, et al. (1997) LMW-PTP is a negative regulator of insulin-mediated mitotic and metabolic signalling. *Biochem Biophys Res Commun* 238: 676-682. [Crossref]

8. Seki N, Hashimoto N, Taira M, Yagi S, Yoshida Y, et al. (2007) Regulation of Src homology 2-containing protein tyrosine phosphatase by advanced glycation end products: the role on atherosclerosis in diabetes. *Metabolism* 56: 1591-1598. [[Crossref](#)]
9. Buelt MK, Xu Z, Banaszak LJ, Bernlohr DA (1992) Structural and functional characterization of the phosphorylated adipocyte lipid-binding protein (pp15). *Biochemistry* 31: 3493-3499. [[Crossref](#)]
10. Pandey SK, Yu XX, Watts LM, Michael MD, Sloop KW, et al. (2007) Reduction of low molecular weight protein-tyrosine phosphatase expression improves hyperglycemia and insulin sensitivity in obese mice. *J Biol Chem* 282: 14291-14299. [[Crossref](#)]
11. Matlashewski GJ, Tuck S, Pim D, Lamb P, Schneider J, et al. (1987) Primary structure polymorphism at amino acid residue 72 of human p53. *Mol Cell Biol* 7: 961-963. [[Crossref](#)]
12. Gaulton KJ, Willer CJ, Li Y, Scott LJ, Conneely KN, et al. (2008) Comprehensive association study of type 2 diabetes and related quantitative traits with 222 candidate genes. *Diabetes* 57: 3136-3144. [[Crossref](#)]
13. Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, et al. (2009) A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nat Med* 15: 1082-1087. [[Crossref](#)]
14. Iannaccone U, Bergamaschi A, Magrini A, Marino G, Bottini N, et al. (2005) Serum glucose concentration and ACP1 genotype in healthy adult subjects. *Metabolism* 54: 891-894. [[Crossref](#)]
15. Ammendola M, Gloria-Bottini F, Sesti F, Piccione E, Bottini E (2008) Association of p53 codon 72 polymorphism with endometriosis. *Fertil Steril* 90: 406-408. [[Crossref](#)]
16. Sokal RR, Rohlf FJ (1981) *Biometry*. NK: Freeman, New York.