Cytosolic Low Molecular Weight Protein-Tyrosine Phosphatase Activity and Clinical Manifestations of Diabetes

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Abstract: *Background:* Biochemical, epidemiological and experimental evidence suggests that cytosolic low molecular weight protein-tyrosine phosphatase (cLMWPTP) genetic variability may have a role in the clinical manifestations of diabetes mellitus. In this article, the authors review data from their laboratory supporting the hypothesis that high cLMWPTP activity favors severe manifestations of diabetes. *Methods:* In 829 type 2 diabetic patients, the authors have studied the association between clinical parameters and cLMWPTP activity. The cLMWPTP genotype was determined in all subjects. *Results:* In diabetic subjects, low activity cLMWPTP protects against extreme increase of glycemic level (patients studied 489). The correlation between glycemic level and glycated hemoglobin concentration is increasing with cLMWPTP activity (patients studied 270). In diabetic subjects with coronary artery disease, left ventricular ejection fraction is negatively correlated with cLMWPTP activity (patients studied 70). *Conclusions:* All these observations point to a negative effect of high cLMWPTP activity on clinical manifestation of diabetes in accordance with theoretical and experimental data and suggest that pharmacological decrease of cLMWPTP activity could have beneficial effects on the clinical evolution of this disease. Moreover, in diabetic subjects with high activity ACP1 genotype, an intensive treatment could help to prevent severe clinical manifestations.

Key Indexing Terms: cLMWPTP; Diabetes; Glycemia; Glycated Hb; LVEF. **[Am J Med Sci 2014;347(2):147–150.]**

Biochemical, epidemiological and experimental evidence suggests that cytosolic low molecular weight protein-tyrosine phosphatase (cLMWPTP) genetic variability may have a role in the clinical manifestations of diabetes mellitus. In this article, we review data from our laboratory,[1–4] showing that high activity of cLMWPTP favors severe manifestations of diabetes, thus suggesting that pharmacologic reduction of the enzyme activity may have beneficial effects on the evolution of the disease.

The cLMWPTP encoded by the highly polymorphic locus ACP_1 is a member of the PTPase family and is present in all tissues. All ACP_1 genotypes show 2 main isozymes designated F and S according to their relatively fast and slow anodal electrophoretic mobility, and the ratio of their activities is markedly different among genotypes (Table 1). Significant differences between F and S isoforms have been observed in both enzymatic and molecular properties, suggesting that they perform different physiological functions.[5]

In vitro cLMWPTP is able to hydrolyze phosphotyrosine containing synthetic peptides of the human insulin receptor and of band-3-protein. High cLMWPTP activity may favor high glycemic level through a depression of insulin action. However, because phosphorylation of band-3-protein is associated with increased glycolytic rate through activation of aldolase, phosphofructokinase and glyceraldeyde-3-phosphate dehydrogenase,[6] high cLMWPTP activity may favor high glycemic level through a decrease of activity of glycolytic enzymes. The enzyme is also able to dephosphorylate flavin mononucleotide, contributing to the concentration of FAD and in turn to regulation of flavoenzymes activity important for the metabolic output.

These biochemical and functional properties of cLMWPTP suggest a relevance in glucose metabolism and an important role in the clinical manifestations of diabetes mellitus. Indeed, early observations in diabetic pregnant women from the population of Rome have shown that women with high glycemic level (greater than 8.9 mmol/L) have a very low proportion of genotypes carrying the *A allele, which is associated with the lowest enzymatic activity. The pattern of association was similar in gestational and preexisting diabetes (type 1 diabetes and type 2 diabetes [T2D]).[1]

Direct evidence of the role of cLMWPTP in regulation of glycemic level is given by the experimental study by Pandey et al,[7] showing that a reduction of ACP_1 expression by antisense oligonucleotide improves hyperglycemia and insulin sensitivity in obese mice.

Recent studies suggest that glycosylated products and glucose have an important role in the pathogenesis of atherosclerosis, stimulating the proliferation of smooth muscle cells: protein phosphatases have an important role in regulating these effects on smooth muscle cells.[8,9]

MATERIAL AND METHODS

The data on 829 adult diabetic subjects were reviewed.[1–4] Written informed consent was obtained by the patients to participate in this investigation that was approved by Institutional Review Board.

Statistical analyses were performed by commercial software (SPSS; SPSS, Chicago, IL).

RESULTS AND INTERPRETATION

cLMWPTP Activity and Glycemic Control in Diabetic Patients

Figure 1 shows a statistically significant negative correlation between glycemic level and proportion of low activity genotypes of cLMWPTP in diabetic subjects pointing to a protective action of low cLMWPTP activity against extreme increase of glycemic level. The figure includes T2D, type 1 diabetes and gestational diabetes.[1,2]

The association between the degree of glycemic control and cLMWPTP has been observed in all classes of diabetic disorders; it, therefore, seems unlikely that the association may represent a mere chance-sampling artifact.

The glycemic level is the end result of endogenous and exogenous factors, depending on both the basic severity of the disease and on the therapeutical efforts. cLMWPTP genotype is

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TABLE 1. F and S isoform concentrations in relation to the cLMWPTP genotype[10]

Total quantity of F		Total quantity of S	
*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

a characteristic determined at the time of zygote formation and, as such, cannot depend either on the severity of disease or on the therapy provided. Conversely, cLMWPTP might influence the severity of disease, intensity of therapy required or both. The present data indicate that at least 1 of these mechanisms is operating.

Diabetes might influence cLMWPTP phenotypic activity as well: this seems worth investigating. We would stress that, however, such possibility has no bearing on the interpretation of data in Figure 1. Because cLMWPTP activity was assigned on the basis of genotype, the association represents a statistical relation of glycemic level with cLMWPTP genotype and can be interpreted in the direction "cLMWPTP1 genotype → glycemic level" and only in this direction.

cLMWPTP Activity and the Relationship Between Glycemic Level and Glycated Hemoglobin Concentration

At present, the best measure of blood glucose level in clinical practice is glycated hemoglobin (Hb), which measures the percentage of Hb molecules that have undergone glycation. Correlation analysis, however, indicates that only about one third of glycated Hb variance is explained by blood glucose variance, suggesting that other factors influence the level of glycated Hb and probably of other proteins too. The subjects studied represent a random sample from several thousand diabetic patients under scheduled control in the Center for Diabetes of the Hospital. Glucose and glycosylated Hb levels are generally stable in the course of month in each patient; thus, a possible bias in the correlation between the 2 variables seems unlikely.

It is likely that most diabetic complications are related to glycation of structural and enzymatic proteins. Therefore, if glycation is dependent not only on glucose level but also on genetic factors, at comparable levels of blood glucose, in the presence of these factors, higher glycation level of proteins could be attained leading to clinical disease and more severe complications.

Figure 2 shows that the proportion of glycated Hb variance explained by glycemic level is increasing with cLMWPTP activity,[3] suggesting that the damage of Hb and probably of other structural and enzymatic proteins by glucose is more efficient at comparable levels of glycemic values in presence of high cLMWPTP activity.

Left Ventricular Ejection Fraction and cLMWPTP Activity in T2D Patients With Coronary Artery Disease

Table 2 shows that left ventricular ejection fraction (LVEF) is negatively correlated with total cLMWPTP activity. Such correlation is very marked with S isoform activity (Figure 3), and it is not significant with F isoform activity.

The pattern of association is compatible with the hypothesis of more severe damage of cellular structures induced by high glucose levels in presence of high cLMWPTP activity.

Negative effects on myocyte glucose metabolism related to decreased glucose utilization and/or to decreased activity of flavoenzymes because of increased dephosphorylation of insulin receptors and/or increased dephosphorylation of flavin mononucleotide represent another possibility. Such possibility, however, is compatible with the damage to cellular structures.

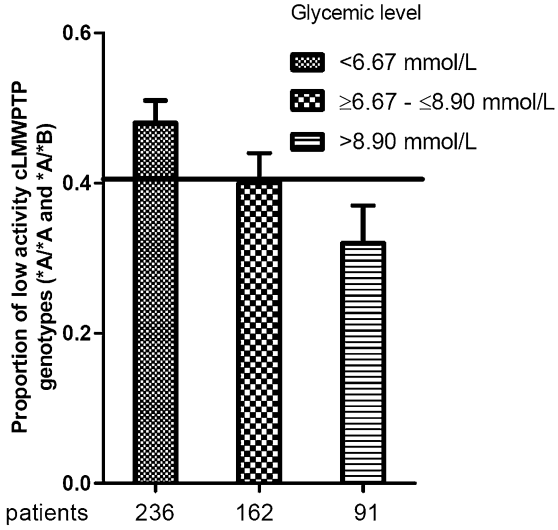

FIGURE 1. Proportion of low activity cLMWPTP genotypes (*A/*A and *A/*B) in relation to fasting glycemic level in diabetic subjects. In healthy controls, the proportion of *A/*A and *A/*B genotypes is 40.7%. Linear correlation, $P = 0.009$. The figure shows a negative correlation between glycemic level and proportion of low activity cLMWPTP genotypes. The horizontal line corresponds to low activity (*A/*A and *A/*B) cLMWPTP genotypes.

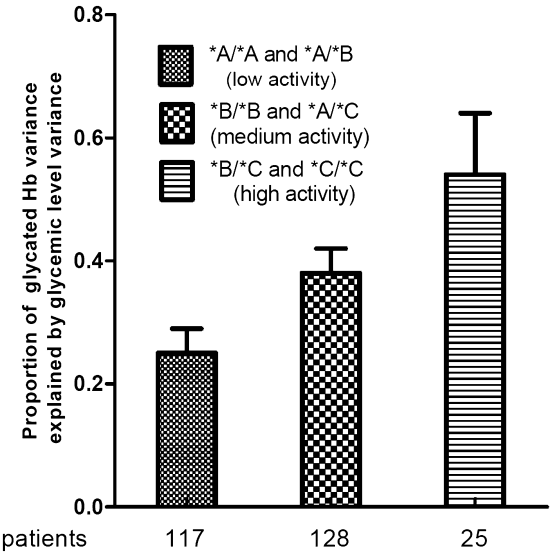

FIGURE 2. Proportion of glycated Hb variance explained by glycemic level variance in relation to cLMWPTP activity. This is estimated by the square of correlation coefficient. The figure shows that the proportion of glycated HB variance explained by glycemic level increases with cLMPTP activity.