Plasma Gamma-Glutamyltransferase (GGT) Activity in Inflammatory Bowel Disease: Is the Clinical Laboratory Plasma GGT Assay Sensitive Enough for Gastroenterology?

To the Editor:

A recent study[1] reports the association between polymorphisms of genes regulating plasma gamma-glutamyltransferase (GGT) activity and the risk of diabetes, cardiovascular, and other diseases, including inflammatory bowel disease (IBD). As remarked by the authors, the function of GGT is to make cysteine available for the synthesis of intracellular glutathione, thus a decrease in GGT gene expression may lead to decreased glutathione availability and may impair the efficiency of antioxidant defenses; this interpretation is in contrast with the fact that, in the case of diabetes and coronary atherosclerosis, the diseases are associated with increased values of plasma GGT rather than decreased values,[2] and no disease has yet been associated with decreased levels of plasma GGT. In IBD a decrease in GGT activity in the inflamed intestinal mucosa has been reported,[3] but a correlation between plasma GGT levels and IBD has never been found.

To check whether this might depend on the modest sensitivity and reproducibility of the current clinical assay for GGT, we analyzed plasma samples from a small cohort of 48 subjects with IBD (27 Crohn's disease and 21 ulcerative colitis) and 48 healthy subjects, matched for age and gender (Table 1). When the samples were assayed by the current routine clinical laboratory procedure, based on the hydrolysis of the chromogen gamma-glutamyl-3-carboxy-4-nitroanilide,[4] we did not find any difference between IBD patients and controls.

TABLE 1. Characteristics of Subjects with Inflammatory Bowel Disease (IBD).

	Controls (n=48)	IBD (n=48)	P Controls vs. IBD
Males, *n*	31	31	
Age, years	35.0 (28.0–48.5)	35.5 (26.5–48.5)	n.s.
Calprotectin, μg/g	N.A.	224.5 (81.5–423.5)	
CRP, mg/L	0.08 (0.04–0.14)	1.04 (0.40–4.31)	< 0.05
ESR 1h, mm/h	N.A.	16.0 (8.0–31.0)	
Total GGT, U/L *	18.3 (13.3–24.8)	14.9 (11.1–21.0)	n.s.
b-GGT, U/L *	1.4 (0.9–2.4)	1.7 (0.9–2.8)	n.s.
m-GGT, U/L *	0.5 (0.3–0.9)	0.2 (0.1–0.4)	< 0.0001
s-GGT, U/L *	5.4 (2.8–8.8)	3.9 (2.6–7.6)	n.s.
f-GGT, U/L	10.0 (8.3–13.5)	8.4 (6.2–10.5)	< 0.01

Data presented are median (25th-75th percentile). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyltransferase. Statistical analysis: Student's t*-test; *statistical analysis performed on ln-transformed data. n.s., not significant; N.A., not available.*

We then repeated the analysis with a high sensitivity fluorescent assay,[5] which allows the separate determination of the four GGT fractions present in human blood: b-GGT (molecular weight [MW] 2000 kDa), m-GGT, (MW 1000 kDa), s-GGT (MW 140 kDa), and f-GGT (MW 70 kDa).

By this method we found that two of the four fractions, m-GGT and f-GGT, were significantly reduced in IBD as compared with controls (Table 1). Within the group with IBD, no correlation emerged by Pearson's correlation analysis between the values of these fractions and the levels of fecal calprotectin, C-reactive protein (CRP), erythrocyte sedimentation rate, or therapy, thus suggesting that reduced m-GGT and f-GGT are a trait of the disease, and not a consequence of its clinical activity.

To our knowledge, this is the first report concerning the association between low plasma GGT activity and IBD, confirming the results of the study by Middelberg et al,[1] and the first associating a human disease with decreased values of GGT, rather than increased values. The low sensitivity of the routine clinical assay for GGT seems to impair its diagnostic value and needs to be overcome, possibly opening new perspectives for the study of the many diseases associated with polymorphisms regulating GGT expression, and IBD in particular.

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