

## LETTER

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# Benign Pancreatic Hyperenzymemia or Gullo's Syndrome

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Dear Sir:

I read the recent paper by Frulloni *et al.* [1] on pancreatic hyperenzymemia with interest. These investigators undertook a review of many papers published on this topic, discussing the clinical significance of both pancreatic and extrapancreatic hyperenzymemia. They also discussed the condition of pancreatic hyperenzymemia without apparent causes. However, in this context, they cited my paper on familial pancreatic hyperenzymemia [2] but not my previous study on sporadic pancreatic hyperenzymemia [3]. I believe that this second paper should have been mentioned in a review of the literature on pancreatic hyperenzymemia, above all, because this was the first study on benign pancreatic hyperenzymemia. In this study, I demonstrated that healthy subjects, without any pancreatic disease, with clinical, laboratory and pancreatic function tests, ultrasound, computed tomography and retrograde cholangiopancreatography all absolutely normal, can have pancreatic hyperenzymemia, which generally presents considerable fluctuations, including periods of normalization. Most of these subjects were followed by me for many years and they continued to have pancreatic hyperenzymemia and continued to be without any pancreatic disease.

The results of this study [3] were questioned by the same authors of the above-mentioned article in a letter to the editor [4] which appeared after the publication of my paper.

This letter reported a group of 30 healthy subjects, of whom 16 had hyperamylasemia alone and the remaining 14 hyperamylasemia and hyperlipasemia; in addition, 13 of these 30 subjects also had hypercholesterolemia and/or hypertriglyceridemia. They concluded that the abnormal increase of serum pancreatic enzymes in these subjects was due to pancreatic steatosis caused by the dyslipidemia. The diagnosis of pancreatic steatosis was made by these investigators on the basis of the ultrasonographic finding of a hyperechogenic pancreas. This conclusion is, however, unacceptable, first, because there is no proof that pancreatic steatosis actually exists in humans and, second, because there are no studies which indicate with certainty that the ultrasound finding of a hyperechogenic pancreas is an expression of steatosis or of pancreatic fat infiltration. Moreover, even if the dyslipidemia could actually cause pancreatic steatosis or pancreatic fat infiltration and consequently hyperenzymemia, this would only have occurred in the 13 of the 30 subjects with pancreatic hyperenzymemia that they described, i.e. the 13 who had the dyslipidemia. In the remaining 17 patients in whom there was no dyslipidemia and no other possible cause of pancreatic hyperenzymemia, what was it due to?

They also reported that 24 of the 30 subjects with hyperenzymemia had a hyperechogenic pancreas at ultrasound; 13 of these 24 had dyslipidemia which, in their opinion, was the cause of the hyperechogenic pancreas, but why did the remaining 11 who did not have

dyslipidemia have a hyperechogenic pancreas? Perhaps, had these 11 subjects pancreatic steatosis also which was the cause of their hyperenzymemia? If so, what was the cause of the pancreatic steatosis?

Many of the subjects described by these authors (16 out of 30) only had hyperamylasemia; if there was really steatosis of the pancreatic cells, i.e. "an accumulation of fat inside the pancreatic acinar cell, disturbing exocytosis" as Frulloni *et al.* write in their article [1], should there not also have been an increase in the other pancreatic enzymes, at least in some of them?

In my first paper on pancreatic hyperenzymemia [3], only 3 of the 18 subjects with this anomaly had hypercholesterolemia and, on the basis of this work and of all my subsequent experience on this topic, I believe that the dyslipidemia does not have any role in the serum increase of the pancreatic enzymes, at least not in this syndrome which I described.

In addition, I have just completed a study in which I used magnetic resonance to assess whether the pancreas of healthy subjects with dyslipidemia and with pancreatic hyperenzymemia is a fatty pancreas, as the above-mentioned authors claim, but I found no signs of fatty infiltration of the pancreas in any of them.

To see whether alterations in the Wirsung duct could explain the hyperenzymemia, we recently evaluated the effect of secretin on the duct in subjects with this benign form of pancreatic hyperenzymemia [5], and we found no alterations in the caliber of the Wirsung duct which could explain the enzymatic alteration.

In another recent study [6], we assessed whether mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene may have a role in the etiology of this form of hyperenzymemia. We found that the frequencies of the mutations detected in subjects with pancreatic hyperenzymemia were similar to those in the general Italian population which excludes a role of this gene in the etiology of this hyperenzymemia.

I have seen and continue to see several healthy subjects with sporadic or familial benign pancreatic hyperenzymemia. I believe that this is a new syndrome which I am the first to have described. The pathogenesis of this anomaly remains to be clarified.

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## REPLY

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Dear Sir,

We thank Dr. Gullo for his comment on our paper recently published [1].

First of all, we would again like to emphasize that an increase of serum pancreatic enzyme (amylase and/or lipase) in asymptomatic patients may be a laboratory finding without clinical significance or a manifestation of extra-pancreatic diseases, but it may also be related to pancreatic damage. Our clinical experience together with some previously published papers [2, 3, 4] and an in-progress work by our group suggest that, in a variable percentage of cases, asymptomatic hyperamylasemia and/or hyperlipasemia may be the first biochemical sign of pancreatic involvement by an inflammatory or neoplastic process. Probably, this is not so common as has recently been reported (more than 50% of cases) [2], but pancreatic disease can be found in a significant percentage of cases. For example, long standing hyperamylasemia (up to 7 years) is often present in patients affected by intraductal papillary mucinous neoplasms [5, 6], probably secondary to partial or complete occlusion of the main or secondary pancreatic ducts by mucin.

Secondly, pancreatic steatosis, namely the presence of lipid droplets in the acinar cells of the pancreas, has been observed both in animals [2, 7, 8, 9, 10, 11] and in humans [12, 13, 14, 15]. The pathogenesis of pancreatic steatosis has not been defined, but malnutrition [7, 10, 12] and alcohol abuse [7, 12, 13] have been implicated in the pathogenesis. We postulated that dyslipidemia may also be a cause of intra-acinar accumulation of lipids (similarly to hepatic steatosis). Therefore, pancreatic steatosis in "some" patients with pancreatic hyperenzymemia and dyslipidemia may alter intracellular exocytosis. Our preliminary results in an ongoing study seem to confirm that the content of lipids in the pancreas quantified by MR in "some" patients with hypercholesterolemia and/or hypertriglycerid-

emia and serum pancreatic hyperenzymemia is higher than in normal controls.

Finally, Dr. Gullo asked why we detect only an increase of serum pancreatic amylase and not other serum pancreatic enzymes. Currently, in clinical practice, we determine only serum pancreatic amylase instead of lipase, and, as stressed in the paper, we may observe an increase in both serum pancreatic enzymes. However, in some cases only hyperamylasemia or hyperlipasemia may be observed and we do not have an answer for this. We can only observe that a serum increase of only one hepatic enzyme may be documented in hepatic steatosis [16].

In conclusion, we agree that sporadic pancreatic hyperenzymemia may be a benign syndrome without clinical significance, but in clinical practice we should consider that it may represent a biochemical sign of disease, including pancreatic disease.

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Immanuel Kant

(Image from <http://en.wikipedia.org/>)

As a brief comment to these letters, the Editors would like to recall a sentence of Immanuel Kant (1724-1804):

.... Ich sehe dennach nichts Besseres für mich, als die Methode der Ärzte nachzuahmen, welche glauben, ihrem Patienten sehr viel genutzt zu haben, wenn sie seiner Krankheit einen Namen geben,....

“... Therefore, for me there is no better way than to imitate the method of those doctors who believe they have been very useful to their patient for having given a name to his illness, ...”

(From “Versuch über die Krankheiten des Kopfes, 1764. In: Kant’s Werke, Band II - Gesammelte Schriften, Vorkritische Schriften II, 1757-1777. Berlin: Druck und Verlag von Georg Reimer, Neudruck 1912:260 (Erste Auflage 1905).