Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus

To the Editor

I read with interest the article titled "Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus".[1] It appears that neither the sample size nor the results presented justified, to some extent, the conclusion drawn by the authors. Hereby, I would like to elaborate important points and certain pitfalls from a Clinical Biochemist point of view in concern with 2 targets: validity of insulin measurement in evaluating the diabetic state and possible link of diabetic control with serum pancreatic enzymes.

Diabetes mellitus is the world's most prevalent metabolic disorder and an ever-growing burden on medical care resources. Hence, studies that deal with diabetic medicine have to include large numbers of patients as is the case in clinical trials and epidemiological studies. The authors assessed biochemically only 14 of type 1 diabetics, mean ± standard deviation (SD) was 9.8 ± 6.2 µU/ml and 25 of type 2 diabetics, mean ± SD was 11.3 ± 5.4 µU/ml as well as 20 controls, mean ± SD was 10 ± 3.8 µU/ml with no significant differences being observed in serum insulin. Despite this, the classification was based according to insulin levels. From a pathophysiological state, serum insulin is usually very low or undetectable in type 1 and low, normal or elevated in type 2 diabetics,[2] a classical pattern that did not exist in Aughsteen et al[1] series of patients. This is not unexpected particularly when the analytical and biological variables influencing insulin status are considered.

Several factors affect the validity of insulin values and their usefulness in clinical practice.[3] Insulin is secreted by the pancreatic β-islets of Langerhans and upon its first passage through the liver, a large and variable extent of it is taken up by the liver (first passage substance) and, hence, peripheral blood level of insulin is not an actual representative of its actual secretion. It has a short half life of 4 minutes with a pulsatile fashion of secretion. In addition, exogenous therapeutic insulin as well as insulin antibodies (as in type 1 diabetics) are known cross reactants in certain analytical kits. These constructing factors may point to the usefulness of measuring C.peptide as an indicator of endogenous insulin secretary state. C.peptide is secreted with insulin in equimolar quantities, has a longer half life of 33 minutes, is not sequestered by the liver and can be measured in the presence of exogenous insulin or insulin antibodies. Peripheral concentration of C.peptide may, therefore, more accurately reflect β-cell insulin secretion rate. Hence, C.peptide has a potential application when measured with insulin for assessing residual β-islets reserve (as in type 1 diabetics) and also for investigating inappropriate insulin secretion (as in insulinoma) or intake (as in factitious hypoglycemia). These are the clinical situations where measurement of C.peptide with or without insulin or proinsulin (β-cell polypeptides family) is commonly requested.[4] In diabetic care, for the assessment of glycemic state, it has been traditionally accepted to rely on glycosylated hemoglobin (HbA1c) and plasma glucose rather than on insulin.[5] However, the authors didn't make use of the data available from these glycemic indicators and shifted their interpretation to insulin levels, an unusual trend in diabetology.

For assessment of exocrine pancreatic function, the authors presented the percentage decline in amylase and lipase activities taking the mean level of the control subjects as the presumed cut-off. However, the biological variation (within-individual and between-individuals) that affect all biochemical parameters makes such selected point as an index of normality an inapplicable issue. All these factors may weaken the statistical significance of the data which already showed scattered pattern. Finally, the authors focused on attributing the decline in mean enzymes activities to be solely due to insulin deficiency based on their previous in vivo study.[6] However, no mention was made regarding the possible effect of cholecystokinin-pancreozymin hormone secreted by F cells of pancreas which controls the secretion of pancreatic enzymes.[7] An impairment of this pancreatic hormone per sec or as a consequence of paracrine effect of insulin deficiency or glucagon excess in diabetes is worth to be considered and investigated.

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Reply from the Author

I kindly appreciate Professor Waad-Allah S. Mula-Abed interest and criticisms on the results and conclusions of our article entitled; Biochemical Analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes

mellitus, published in Saudi Med J 2005; 26: 73-77. Although, the comments seem to be rather aggressive, it is of my pleasure to clarify and argue all his doubts and queries

1) I do agree with Prof Waad-Allah's concern on the limited number of diabetic patients included in the study. The sample size of type 1 and type 2 diabetics is rather low but statistically representative. The reason for this is one of the major difficulties facing researcher in 3rd world countries, especially finding an easy access to research needs. Being an anatomist researching in the field of experimental and human diabetes for more than 20 years, and not attached to a hospital, I face a great difficulty in obtaining the desired number of diabetic cases for my research. The type 1 and type 2 diabetic cases included in our study were collected from those known diabetic patients referred to a private medical laboratory in Amman, Jordan during 8 months period (from April to November 2003). The only point I was concerned about during evaluation process of the article by Saudi Med J was the limited number of diabetic cases. On the other hand, the point raised by Prof. Waad-Allah on the number of control cases is unacceptable, as 20 cases for control is adequately representative. I do hope the Professor will be helpful in securing adequate number of diabetic cases in a joined future research on diabetes if he is interested.

2) Prof. Waad-Allah's comment on insulin level being a base for categorizing our diabetic patients into type 1 and type 2 is wrong. It is clearly stated in the abstract and materials and methods of the article that our classification was based on the age onset and the type of received treatment before analyzing blood samples for serum insulin in both types of diabetics.

Prof. Waad-Allah evaluated the no significances statistical difference of mean values of serum insulin levels between normal, type 1 and type 2 diabetics as a pitfall. I would like to stress here that the estimates of serum insulin for both types of diabetes (clearly indicated in the article) were presented as means ± SD not as single value per each patient. This is quiet obvious, if the professor had realized a rather high SD estimates for the mean insulin values. This SD values would certainly be lowered if we were able to include more number of diabetic patients in our study. I would like to assure Prof. Waad-Allah that the estimates of serum insulin between individual patients screened in our study were so variable. In type 1 diabetics, the insulin estimates ranged between 0.7–18.6 µU/ml for males, and 5-16.9 µU/ml for females, while in type 2 diabetics, it ranged between 0.35-18.8 µU/ml for males, and 3.7-17.9 µU/ml for females. If Prof. Waad-Allah is interested, it will be of my great pleasure to provide him with detailed data of each normal and diabetic case examined in our study to justify what he had commented on insulin values being very low in type 1 diabetes, and being low, normal or elevated in type 2 diabetes.

3) I do agree with Prof. Waad-Allah that C-peptide level will omit the influence of the administered exogenous insulin. The estimation of C-peptide was carefully considered prior to conducting our research, but it was excluded due to its cost, as we all know that research grants are few and limited.

4) Prof Waad-Allah has also commented that it is more justified to rely on HbA1C and plasma glucose rather than on insulin in evaluating exocrine pancreatic insufficiency. I would like to stress here that in our article we presented the reduction in serum amylase and lipase activities in comparison with serum insulin levels and with the duration of illness. I am sure from our data that Prof. Waad-Allah will have certainly be convinced with what he had puzzled if we had presented the reduction of pancreatic enzymes in relation to HbA1C and glucose values. The research article should consider the directly related parameters, which in our study proposal was based on insulin factor and duration of illness for type 1 and type 2 diabetes. Actually, our aim in the article was to emphasize the reduction in pancreatic enzyme activity (synthesis) in diabetic patients.

5) Prof. Waad-Allah also has commented that we had only focused on the decline in serum insulin level as a major factor for amylase and lipase impairment and ignored the influence of impaired pancreozymin cholecystokinin (CCK) level and elevated glucagons level. I would like to ask Prof. Waad-Allah as to which reference he based to claim that CCK (previously called cholecystokinin-pancreozymin) is produced by pancreatic F cells, as to best of my knowledge, CCK is produced by upper duodenal mucosa. A CCK hormone stimulates pancreatic enzymes release (not synthesis) via specific acinar cell receptors, which may be an additional factor in lowering enzymes level. This point had thoroughly been considered in my previously published work. Also, CCK is believed to have stimulant effect on insulin synthesis by beta cells either directly or via neural mechanism. The relation of glucagons with pancreatic enzymes synthesis is rather unclear and unjustified in large body of pancreatic research. I would like to remind the Professor that I am writing a research article not a PhD thesis. Finally, Prof. Waad-Allah seems unhappy with our suggestion that estimation of pancreatic enzymes might be essential for evaluating chronicity of diabetes and response to treatment.

The aim of our conclusion is opened for diabetic clinicians to be considered or not. We as researchers illustrate results and conclusions of our analysis and open it for discussion and consideration.

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