Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Effect of Deranged Thyroid Profile on Glycated Hemoglobin : Pre and Post Treatment

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Sir — The authors have done a wonderful study regarding the "Effect of Deranged Thyroid Profile on Glycated Haemoglobin : Pre and Post Treatment". It has been rightly pointed out that thyroid disorders can have a significant effect on blood glucose levels and, if left untreated, can affect glycemic control. Hyperthyroidism has long been recognised to promote hyperglycaemia. There also exists a relationship between insulin resistance and oxidative stress. The interrelationship between thyroid dysfunction and insulin resistance has also been established by some studies that have shown normalisation of long-term indicators of glycemic controls (HbA1c) among non- diabetic thyroid disorder patients following thyroxine replacement therapy.Thus, normalisation of HbA1c values in such patients by only treating their thyroid dysfunction can clearly decrease the diabetic burden to a great extent.

In this regard the editor has correctly commented that, one should be cautious in interpretation of HbA1c values in patients suffering from thyroid dysfunction as they may be falsely elevated in untreated hypothyroid patients (who have found to have normal fasting and post prandial blood glucose levels), which was found to be normalised on levothyroxine replacement therapy.

On the other hand, patients with hyperthyroidism do not show such correlation between glycated haemoglobin levels and thyroid hormone levels both pre and post treatment.

So tests like serum fructosamine assay and glyclated albumin have been proposed to overcome this fallacy.

This study has brought to light the need to such larger scale studies to understand the pathophysiology behind the false elevation of HbA1c in overt hypothyroidism.

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Best Practices In D-Dimer Testing; In COVID-19 and Beyond : Expert Group Recommendations

Sir — The early part of year 2020 witnessed the evolution of D-dimer as one of the most vital laboratory parameters in the management of COVID-19; the clinicians and laboratorians ensured an intense usage in the testing and clinical utilization of D-dimer. A parameter, often less utilized and even lesser understood, stood in the driving seat of predictive value pertaining to risk and prognosis around COVID-19 associated coagulopathy. Whilst always considered as a VTE exclusion parameter, and sometimes used in sepsis, it was evidenced to be of immense use in evaluating and managing a disease which was over a year old and already caused a damage of decades. Never had, in the history of hemostasis parameters, a test become so common that it evolved as a over the counter (OTC) test parameter. These developments also presented a major challenge as to how to appropriately interpret and use the values of this incredible parameter, particularity with the growing utilization of the parameter, within and beyond COVID-19. D-dimer, now, and often, is being ordered as a walk-in test parameter, follow up test parameter, "test package" parameter and even a establish / rule out test parameter of COVID-19 as such, we wonder if the depth of knowledge around it can support the adequate and appropriate utilization of this wonder parameter. Here is an attempt to revisit and put together the recommendations on the best practices around D-dimer testing, particularity in the post COVID era, not only to counter the challenges in D-Dimer testing but also to ensure that D-dimer joins the league of Prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen as the basic minimum tests done at any hemostasis laboratory.

D-dimer is a fibrin split product derived from the plasmin-mediated degradation of cross-linked fibrin formed due to thrombin. D-dimer can hence be considered a biomarker of clot/thrombus formation and intravascular coagulation (DIC).

Blood sample for D-dimer should be collected in 3.2% Trisodium Citrate Anticoagulant (9:1) followed by Heparin and EDTA (CLSI and WHO). *Serum samples are unsuitable since it obtained from clotted blood in tubes containing clot activators which could increase products of thrombin (fibrin breakdown).*

The routine reporting units of D-dimer are ng/mL, ìg/L, ìg/mL, or mg/L. *Theoretically they can further be expressed in DDU and FEU*. Among the measure units that can be adopted, "mg/L" (or "ng/mL") is probably the unit that best approximates the International System (IS). (For sake of example, a value of 500 ng/mL is same as 0.5 ug/mL which is same as 500 ug/L and same as 0.5 mg/L.). *Although, FEU is roughly double of DDU, the practice of conversion from DDU to FEU and vice versa is not recommended.*

D-dimer values are not transferable/comparable between methods and equipments.

There is no WHO / International Reference standard (IS) forD-dimer. The reference range/cut-off value for D-dimer is ideally established by the performing laboratory, or, if a cut-off value published in the literature is used, the value has to be verified and accepted by the users (*those ordering the test*).

Higher values may be observed in liver disease, inflammation, infections (including ARDS), malignancy, trauma, pregnancy, recent surgery as well as advanced age. These high levels in D-dimer could be physiological

like in pregnancy or due to the pathophysiology of the condition itself but D-dimer is not routinely used in these conditions either for diagnosis or in the assessment of its progress except when suspecting venous thromboembolism (*wherein a higher cut-off will be required before ruling out VTE)* or intravascular coagulation (*for calculating DIC score*).

Significant lower D dimer values may be observed if the sample is taken either too early after thrombus formation or if testing is delayed beyond the recommended time duration.

Pre-analytical variables affect D-dimer values. Proper sampling techniques, transportation and centrifugation procedures as per recommendations need to be followed as per recommendations and guidelines.

D-dimer values typically increase in parallel with aging, Adjusting the D-dimer cut-off values to the age of outpatients >50 years increases specificity while hardly affecting sensitivity.

It has been observed that heterophilic antibodies may occasionally develop after infection by rubella, measles, adenovirus, entero-virus, and varicella-zoster viruses. These may be associated with raised D dimer levels.

An isolatedelevation of D-dimer should always be interpreted with caution (assessment of clinical probability).

D-dimer in COVID-19 :

- The upper reference range / cut-off, mentioned in most of the reports, is valid for Venous Thromboembolism.
- The scientific knowledge and clinical evidence around coagulopathy in COVID-19 is still evolving and hence the use of D-dimer as a vital component of evaluation and management should be best correlated with available data.
- There are fair chances of interference with known entities (such as heterophilic antibodies and substances in patient sample) as well as unknown entities (this disease being very new in terms of available data)
- The D-dimer test value needs to be interpreted in context of the clinical profile of the patient, other coagulation and inflammation parameters (although they may not always correlate) as well as previous values/future values on the same platform.
- Comparing D-dimer values across different labs or analysers should be discouraged since it is highly likely that the values (number) will not match.
- Sometime, D-dimer can be the only laboratory parameter elevated in the early stages of disease and it may be so even ahead of any clinical signs and symptoms. Similarly, D-dimer may remain elevated in the terminal stages of illness and even in the convalescence phase when all other parameters might be within normal limits.
- D-dimer should NOT be used as a sole criterion to start therapeutic thromboprophylaxis or perform radiological examination to evaluate evolving thromboembolism. Similarly, anticoagulant therapy should NOT be intensified based only on the biomarkers like D-dimer.

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