JOURNAL OF CURRENT TRENDS IN CLINICAL MEDICINE & LABORATORY BIOCHEMISTRY

Oxidative Stress : The Dominion Editor-In-Chief of Atherosclerotic Dogma

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As it would be a first editorial for me and the journal JCTMB as well, my attempt to come new/creative in editing/redefining the term oxidative stress (OxS) ended only to adopt its previously well established definition of homeostatic disequilibrium between free radicals (FRs) and their contrast counterparts; antioxidants (ANTs). OxS manifests either due to increased generation of FRs and or by decreased ANTs systems that combat the former when in excess. The FRs includes derivatives of Oxygen and Nitrogen Respectively known as Oxygen Reactive Species (ORS) and nitrogen reactive species (NRS). The ANTs are of both enzymic and non-enzymic nature and are engaged in combating excess FRs, maintaining normal physiology and health. The phenomenon of OxS results in both structural and functional damage to important biomolecules viz. Lipids, proteins and nucleic acids leading to disease pathology and the development of disease associated complications [1].

The prevalence of type2 diabetes mellitus (DM) and the metabolic syndrome (MetS) is increasing in developed and developing Countries like India. These patients are at high risk of developing micro and macro vascular complications with 200% greater cardiovascular disease (CVD) risk than non diabetic individuals [2].

Research on FRs and their contrary 'wise' counterparts (ANTs) in biology and medicine is of much importance among bio-medical scientists globally. The phenomenon of OxS in DM, MetS and associated complications has been a topic of intense research for over many years. The precise effect-cause relationship of OxS parameters in these disorders is thus far not clear. Particularly, in the development of related complications, and thus the role of OxS remains to be a topic requiring further research.The progression of DM induces a multiform pathology complicated by a chronic OxS. Thus, it is pivotal in the development of diabetic complications; both micro vascular and cardiovascular [3].

Atherosclerotic cardiovascular disease is the principal cause of mortality in DM and MetS. CVD risk may already be present at the time of diagnosis. The close association of DM with CVD led to the hypothesis that the two arise from a common antecedent "the metabolic syndrome". Although its definition remains to be a dilemma, the common features of "metabolic syndrome" ("syndrome X" or the "insulin resistance syndrome") are central obesity, insulinresistance/hyperinsulinemia, hypertension, and dyslipidemia. Therefore, MetS is an important risk factor for atherosclerotic disease. Insulinresistance is a key link-feature between the MetS and DM. Further, obesity, insulin resistance, and diabetes are associated with a pro-inflammatory state, which is associated with increased cardiovascular risk [4, 5].

In this issue of JCTMB, Kiran et al. reports their study designed to evaluate the status of OxS indicators in identifying FRs damage and ANTs level by measuring lipid peroxidation as malondialdehyde (MDA) and total antioxidant capacity as the ferric reducing ability of plasma (FRAP), respectively [6]. They recruited 50 cases each in DM and MetS groups and the results of OxS variables were compared with that in control group comprising healthy individuals. As expected, OxS status were significantly altered among groups with accelerated MDA and attenuated FRAP levels in both DM and MetS patients compared to controls. Kiran et al. also found that uric acid levels were significantly elevated in both studied groups versus controls. Hyperinsulinemia reduces the renal excretion of uric acid and hyper uricemia reflects insulin resistance, a key pathophysiological factor in MetS. It is of importance that there are studies reported hyperuricemia per se predicts the development of MetS [7]. Although the investigators provided data on dyslipidemia among study groups, there were no correlation analyses done between lipid profile, uric acid and OxS variables in the patient groups [6]. This should be stated as a short coming of the study. Further, measurement of total antioxidant capacity by FRAP does not involve reduced glutathione (GSH), an important major extracellular antioxidant [8]. Therefore, it is required to study GSH to predict additional impairment in ANTs defence system. Furthermore, the reported decrease in the high density lipoprotein cholesterol (HDL) would have been discussed in view of HDL associated decrease in antioxidant capacity owing to its antioxidant and anti-inflammatory properties [9].

More importantly, OxS in diabetes and MetS are importantly considered due to many factors. Of extreme importance are; high glucose, dyslipidemia, obesity, hypertension, and insulin resistance. It is of importance to state my previous research on the association of hyperglycemia with OxS and atherogenic lipidemia in DM [10]. Recently, the role of hyperglycemia inducing OxS and inflammation has been well demonstrated [11].

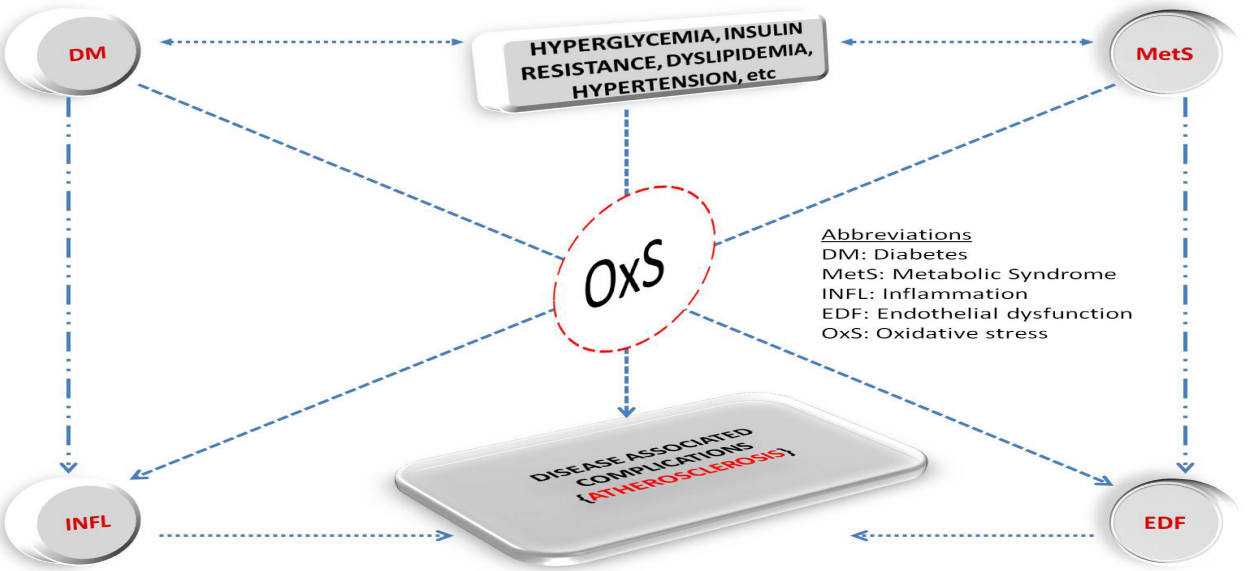

Fig-1. Oxidative stress & Atherosclerotic dogma. ©V.S. Reddy 2014

There is mounting evidence that suggests an intimate relationship of OxS to inflammation (INFL) and endothelial dysfunction (EDF) and interplay among these processes involved with diabetic complications. Insulin resistance per se is resulted in higher production of cytokines linking between INFL, MetS and DM thereby connecting to atherosclerosis [12]. High-sensitivity CRP (hs-CRP) has been demonstrated and used as a marker to predict CVD in MetS. Role of OxS in EDF and atherosclerotic plaque generation has been acknowledged. Nitric oxide (NO) is a vasodilator that exerts positive effects on cardio vasculature. Its consumption or modification by free radicals leads in reduced bio availability and thus EDF [13].

Several authors reported contribution of OxS to INFL, EDF and atherosclerotic risk and is extensively reviewed elsewhere [14-16]. The link between EDF and INFL has also been well documented [17-19]. The role of INFL in EDF and progression of atherosclerosis in DM and MetS has been well researched [20] and reviewed [21-23]. It is clearly evident from the previous literature that an intimate interplay between OxS, INFL and EDF is crucial in developing atherosclerotic complications with OxS playing central role as depicted in Figure-1. In this issue, although Ravi et al. reported OxS well in agreement/support of previous enormous literature in OxS in DM and MetS, Kiran et al. would have also studied INFL and EDF and specific correlations among them enabling improved understanding of OxS mechanisms in the context of associated atherosclerotic complications.

In aggregate, all these factors, in my view, represent atherosclerotic dogma with OxS as its dominion (Figure-1). Thus, I think calling OxS as a dominion Editor-In Chief of atherosclerotic dogma in DM and MetS.

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