EDITORIAL

Rheuminations

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I'll be honest…it has been 35+ years since I started Medical School [MBBS]. And in the realm of Medicine at large, and Immunology/Rheumatology in specific, we are still struggling to find a 'cure' for chronic systemic inflammatory immune-mediated diseases also known as 'autoimmune rheumatic diseases (ARD)'. Rheumatology is still in its cradle having gotten the recognition as a subspecialty of Medicine only in 1972. I have seen the field evolve in terms of understanding the orchestrated 'play' of the immune cells along with cytokines etc. over the past 3 decades, all of which has led to the concept and birth of 'biologic' disease modifying anti-rheumatic drugs [b-DMARDs]. The first b-DMARD to get approved by the Food and Drugs Administration [FDA] was etanercept, a TNF-alpha receptor fusion protein in 1998. Infliximab, a chimeric monoclonal antibody against TNF soon followed in 1999. Ever since then, there has been a flurry of b-DMARDs including 3 more in the same family of TNF-antagonists, 2 in the Interleukin [IL]-6 antagonist class, 1 blocker of the second co-stimulatory T-cell signaling: CTLA-4Ig, 3 IL-1 antagonists, B-cell depleting chimeric monoclonal antibody directed against CD-20 etc. Also, 3 oral Janus-kinase inhibitors have joined the 'gang' and are called targeted synthetic DMARDs.

I still remember the pre-b-DMARD era when rip roaring rheumatoid arthritis was still around, and with my Ustaad Saheb (Mentor), all what we had to offer pharmaceutically were the conventional synthetic [cs] DMARDs including methotrexate, hydroxychloroquine, sulfasalazine, leflunomide and [the younger generation can hold their breath] cyclosporine, d-penicillamine, chlorambucil…GOLD injections and even cyclophosphamide! Corticosteroids have been around since 1950! The 1st and "*so far*" […well, I/You might be next one!] the only Nobel Prize winning revelation in the realm of Rheumatology.

The availability of the b-DMARDs has changed the entire paradigm of pharmaceutical treatment in Rheumatology. They are all quite effective yet extremely expensive making them literally unaffordable in the parts of the world, where health-insurance coverage is suboptimal/non-existent, more so, given the indefinite duration of therapy. Although the b-DMARDs tend to target a specific pathway in the immune system, they are still fraught with some rather challenging adverse drug effects (ADE) including infections: bacterial, mycobacterial [especially reactivation of tuberculosis, more so, in the parts of the world where this disease is endemic] fungal and from other pathogens; malignancies, increased incidence of cardiovascular and cerebrovascular events, thromboembolic events etc. All in all, b-DMARDs are a double-edged sword! They all come with 'a price to pay'!

Now, let's reflect upon the burden of ARD in the community. Rheumatoid arthritis, a potentially crippling and life-threatening disease affects at least 1% of the population, with more than 13 million patients in America itself! Axial and peripheral spondyloarthritis is now being recognized more and more. Various other autoimmune diseases including systemic lupus erythematosus, Sjogren's syndrome, scleroderma, autoimmune myopathy including dermatomyositis and polymyositis, vasculitides, and some more novel entities like IgG-4 related disease, checkpoint-inhibitor chemotherapy associated rheumatic diseases: the list continues to grow!

What can be done to prevent, slow, stop and reverse ARD? In fact, the answer is the other side of the question itself! Human body has a tremendous capacity of healing itself! Only, if we are willing to make healthy choices. Truth is Self-effulgent! It does

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not require a lab-proof! However, as 'scientists', we are always inclined to see/measure the outcomes. Well, it is out there now! SYSTEMIC INFLAMMATORY DISEASES CAN BE PREVENTED AND REVERSED!!! Here are the revelations about some of these ailments including coronary heart disease, diabetes mellitus and even prostate cancer from just a few extremely humbling articles published quite recently.

The Lifestyle Heart Trial showed that it is possible to significantly reduce coronary stenoses and risk of cardiac events using aggressive lifestyle changes, and without lipid-lowering medications. A strong dose-response relationship between self-reported adherence and angiographic changes was found, with excellent adherence during the study. Overall, self-reported adherence was highly correlated with percentage of stenosis.[1] It has also been shown that an intense lifestyle treatment can reduce the expenses on cardiac health/procedures drastically.[2] Interestingly, adherence to a whole food plant-based nutritional program was found to be more important than the type of diet consumed. More adherent subjects showed greater improvements in weight and cardiac parameters. Thus, the intensity of the intervention may be more important than the specific diet for weight loss.[3]

By limiting the daily caloric consumption to 600 Calories, decreased pancreatic and liver triacylglycerol stores, improved maximal insulin sensitivity.[4] It's very humbling! The DIETFITS, a 12-month randomized clinical trial demonstrated that epigenetics must be part of the measures assessed in lifestyle diet intervention studies. Diet determines the expression of many genes![5]

The Direct study was the first large rigorous trial to show such success in remission of diabetes in a clinical practice setting. Diabetes-remission was strongly associated with weight loss in a dose response relationship.[6,7]

A fasting-mimicking diet (FMD) demonstrated that the power of dietary interventions may include reprogramming of tissues to restore lost metabolic function, such as beta cells in the pancreas. Once confirmed in humans, this could elevate lifestyle medicine intervention as a 'primary' modality for type 2 diabetes mellitus treatment. Also, should this treatment lead to beta-cell neogenesis in humans, it could make type 1 diabetes mellitus reversible.[8]

From diabetes 'care' to diabetes 'cure': In a seminal article published about 5 years ago, creative ways to implement lifestyle interventions were reiterated. Those services would include coaching, information, and communications technology.[9]

Intensive nutrition and lifestyle changes can even modulate gene expression in the prostate cancer.[10]

So, in a nutshell, ALL chronic lifestyle mediated diseases have systemic inflammation, alteration in the gut microbiome, oxidative stress, allostatic load, and many other features in common! Well, then the answer becomes simple! It is possible to prevent, slow, stop the progression and even reverse all these diseases with 'the exact same' 4-pronged approach: eat well, move more, think right, and love ALL! The sage generational wisdom of Dadi/Nani (grandmothers) has no ADE!

It's work, yes, but 'its works'!

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