Editorial

The dirty dozen of diabetes

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The Stockholm Dirty Dozen

The term "Dirty Dozen" was coined at a convention held in Stockholm in 1995 to describe 12 important persistent organic pollutants (POPs), which were thought to be toxic to human (and animal) health. These POPs were characterized by four features: Persistence, bioaccumulation, potential for long-range environmental impact and toxicity.[1] A later convention ratified this list, adding more to it. However, the term "Dirty Dozen" has struck to the concept of POPs.

Endocrine Disruptor Chemicals

At about the same time, the term endocrine disruptor chemical (EDC) was coined to describe chemicals that interfered with hormone synthesis and action thus producing various endocrine anomalies, including those of the thyroid and gonads.[2] Most of the POPs acted as EDCs, and a few of them were associated with diabetes, obesity and metabolic disorders. Exposure to dichlorodiphenyltrichloroethane (DDT) *in utero* was liked with a higher incidence of diabetes, use of bisphenol A was found to lead to diabetes and obesity, while polychlorinated bisphenol were associated with diabetes and obesity in children exposed prenatally to the same.[3]

Obesogens

A related group of compounds, the "obesogens," which led to obesity in exposed individuals, was also described. The obesogens linked with insulin resistance/diabetes include bisphenol A, diethyl hexyl phthalate, perfluorooctanoate and organotins (tributylin). These chemicals are found in the plastic industry, aerosols and paint industry, among others. Other obesogens that find their way into humans include high-fructose corn syrup, which is used as a sweetener in foods. The term obesogen also includes drugs such as diethylstilboestrol, thiazolidinediones and certain anti-depressants.[4]

The multiplicity of pathogenic mechanism and associations being unearthed in diabetes has meant that the "Dirty Dozen" or "diabetogens" have not received appropriate attention in the current Indian or global medical literature. However, these diabetogens or environmental metabolic disruptors (EMDs) deserve center stage in the study of diabetes. Diabetes, much more so than most other endocrine diseases, is an ecosensitive disease: Its etiology, clinical presentation, management and prognosis are intertwined with the environment, both physical-natural and manmade, as well as human or social.

The Diabetes Anti–Razor

The use of the term "Dirty Dozen" in diabetes extends beyond what has just been discussed. Traditional medical training teaches us to apply Occam's razor wherever possible, trying to find a single etiology, pathogenetic mechanism or explanation for groups of signs and symptoms, which may superficially appear disparate. Diabetes, however, bucks the trend, and is one example where "anti-razors" hold way. Keeping this in mind, we propose a re-look at the pathophysiology of diabetes, which is currently described by the term "Ominous Octet," so elegantly coined by Defronzo.[5]

The Dirty Dozen of Diabetes

We propose the addition of four well-known hormones to the list of players in diabetes to bring the number to 12. All four hormones have adequate biochemical, epidemiological, observational or clinical support to merit inclusion in the list of the Dirty Dozen of Diabetes. Inclusion of all four players is linked with therapeutic implications of

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significant importance for both patients and diabetes care professionals, for both prevention and management of diabetes and associated metabolic complications.

Catecholamines, Including Dopamine

The ninth player that deserves to be mentioned alongside the Ominous Octet is the catecholamine family. Dopamine, which is the catecholamine with highest concentration in the brain, has already been termed "the forgotten felon".[6] The dopamine modulator drug bromocriptine is used for the management of type 2 diabetes in many countries across the world, and has proven cardiovascular safety.[7] The autonomic nervous system is also involved in the modulation of glycemia, in addition to the cerebral resistance described by Defronzo.[5] Stress is linked with the onset of and with poor control in diabetes.[8] Stress has been known to precipitate diabetic ketoacidosis, and diabetes distress is commonly associated with poor control.

Appropriate use of non-pharmacological intervention, such as cognitive behavioral therapy, coping skills training and stress management help in managing diabetes-associated stress and stress-induced hyperglycemia. Judicial use of timed release bromocriptine helps in resetting the sustained hyperdopaminergic tone that is characteristic of many type 2 diabetes patients.

India has rightly been called a hyperadrenergic or dopaminergic nation. As we move forward in development and modernization, we must try and avoid the stress that inevitably accompanies such transition.[9]

Vitamin D

Vitamin D plays an important role in both type 1 and type 2 diabetes. Acting as an immunomodulatory hormone, it decreases pro-inflammatory cytokines, increases anti-inflammatory cytokines, reduces autoimmune insulitis and protects agasinst type 1 diabetes in children exposed to high doses of vitamin D *in utero* or in infancy. In adults, vitamin D is linked with both insulin secretion and insulin sensitivity, and there is a strong body of evidence, which justifies its inclusion in the Diabetes Dirty Dozen.[10]

Epidemiological evidence adds its weight to this recommendation. Low vitamin D levels are associated with a higher prevalence of metabolic syndrome, diabetes, obesity, hypertension, coronary artery disease and stroke.[10]

Being a vitamin D deficient nation, and a country of heliophobes, we can ill afford to neglect the importance of vitamin D deficiency as a diabetogen if we wish to shed the tag of "global diabetes capital."

Renin–Angiotensin System

The classical impression of the renin–angiotensin system (RAS) as a linear cascade limited to proteolysis has been replaced by an understanding of the multiple hormones, enzymes and functions of this complicated system. Apart from its endocrine functions, it has paracrine and autocrine effects, all of which are mediated by both circulating and local RAS. RAS is present in many organs of the body, including the beta cell. RAS–insulin signaling vitamin D cross-talk, which influences insulin secretion, has been documented in the beta cell.[11] Vitamin D deficiency and obesity are also associated with stimulation of RAS activity.[12]

Randomized controlled trials reveal a lower incidence of new-onset diabetes in patients prescribed angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Because of this, and their nephroprotective and cardioprotective effects, these molecules have become drugs of first choice in hypertension associated with diabetes.[13] While, currently, they cannot be recommended for the primary prevention of diabetes, the future holds promise for RAS-based intervention in diabetes care. RAS, therefore, should justifiably be included as part of the Dirty Dozen.

Testosterone

The fourth hormone, which should be added to the list of diabetes players to complete the Dirty Dozen, is testosterone.

Hypogonadism in men is associated with greater visceral fat, as the attenuating effect of androgens on adipogenesis and cytokine production from adipocytes is lost. In diabetes, low levels of FSH may cause lower androgen synthesis through local cytokines and may lose its capacity to do so in diabetes. Mechanistic evidence such as this is buttressed by clinical proof. Studies have shown that low testosterone precedes the onset of diabetes, and androgen deprivation therapy exacerbates insulin resistance/worsens glycemia in prostate cancer patients. As a corollary, androgen replacement in hypogonadal men is found to improve insulin sensitivity/glycemic levels and reduce insulin requirements.[14]

These findings have important therapeutic implications. Physicians should screen for hypogonadism in men with diabetes, while understanding that this condition affects much more than sexuality. Low testosterone levels should

certainly be treated, aiming for high-normal values, but equally certainly should not be over-treated.

Post Script

If there is one disease that wields an anti-razor to Occam's law, it is diabetes. We have highlighted four hormonal players, working in harmony in the diabetes orchestra, to add to the Defronzo's Ominous Octet.

As the Dirty Dozen, including catecholamines, vitamin D, RAS and testosterone, impact our understanding, diagnosis and management of diabetes, there are novel mechanisms being discovered.

A positive association between high iron intake, high hemoglobin and diabetes mellitus has been studied and discussed recently.[15] The exact mechanism of this has been a matter of speculation however. As we go to press, Danish researchers have discovered that increased activity of divalent metal transporter 1 protein damages the beta cell. Removal of this iron transporter has been shown to protect murine models against diabetes.[16] Whether this will be of clinical significance for iron-deficient India is a matter of debate.

Conclusion

The final word regarding the pathophysiology of diabetes is yet to be written. As we accept existence of the Dirty Dozen and perhaps, the Treacherous Thirteen (iron included), we need to utilize every preventive and therapeutic strategy available to us in order to halt the diabetes pandemic. Each of the known pathogenetic mechanisms should be studied and assessed with an open mind for each individual patient in order to achieve the best possible outcomes.

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