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Short Communication

Dysautonomia, Type 2 diabetes and vasculitis

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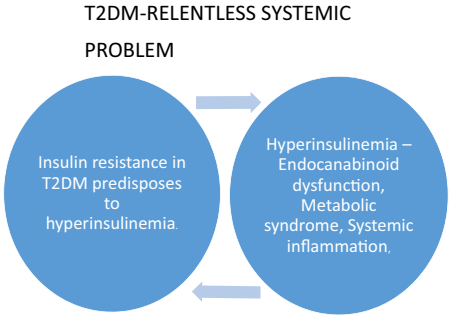
Type 2 diabetes (T2DM) is a relentless systemic problem.

- Coronary artery disease is present in patients with and without high cholesterol particularly in T2DM. Diabetic vasculopathy is a diffuse vascular inflammatory process, not focal.
- High cholesterol is a consequence of metabolic dysfunction similar to elevated blood sugar in T2DM. These abnormalities are secondary to dysautonomia that affects cellular receptor regulation and hormonal release and regulation.
- Vascular atherosclerosis is due to loss of vascular endothelial integrity and systemic inflammation that predisposes to endothelial inflammation and vasculitis. High cholesterol is only a contributor to plaque formation.
- Effect of T2DM on lower extremities is a triple prong effect – affecting arterial capillaries, calf venous system (calf pump) and peripheral nerves (due to dysautonomia). This constitutes classic ''Diabetic Foot.''



1. Dysautonomia/T2DM/vasculitis

- T2DM is a hormonal and metabolic dysfunction due to dysautonomia.
- Clinical complications particularly cardiovascular in T2DM are due to autonomic dysfunction causing vascular endothelial dysfunction, hypercoagulable state, peripheral arterial and venous capillary dysfunction, and cardiac autonomic imbalance.
- Elevated blood sugar is a consequence of dysautonomia. Hypertriglyceridemia and metabolic syndrome are also due to autonomic dysfunction.
- Dysautonomia assessment and treatment is a comprehensive and cost effective approach to T2DM and cardiovascular diseases management.

2. Dysautonomia/T2DM

Type 2 diabetes mellitus, pre-diabetic state and metabolic syndrome are a continuum of clinical process due to underlying autonomic dysfunction.

Impaired incretin release, insulin receptor resistance, and increased hepatic glycogenolysis and gluconeogenesis are the underlying physiologic disorders for T2DM. Increased hepatic fatty acid release and adipose cell dysfunction predisposes to obesity and metabolic dysfunction.

Incretin effect is mediated by several gastrointestinal peptides. Major incretins in humans are GLP-1 (glucagon like peptide) and GIP (glucose dependent insulinotropic polypeptide). Both GLP-1 and GIP are released from intestinal cells in response to nutrient intake. GLP-1 and GIP increase glucose dependent and first phase insulin secretion.

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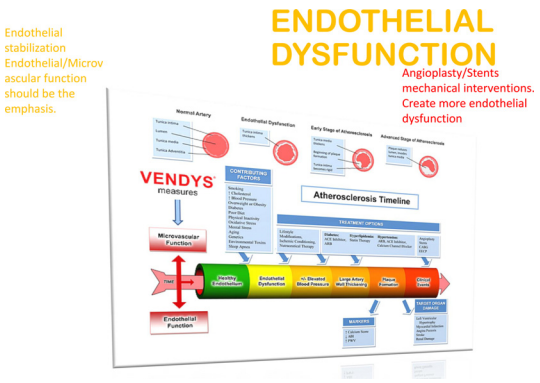
Other systemic effects of incretins include: appetite suppression-direct effect on satiety center, delayed gastric emptying and beta cell neogenesis, and apoptosis inhibition. These features suggest parasympathetic trigger as the underlying mechanism for incretins trigger. Intestinal hormones like systemic hormones are regulated by the autonomic system.

3. Dysautonomia and vasculitis

Vascular endothelium is unique, complex, and has multi-tasking functions. It achieves these functions through modulation of cellular GAP junctions (involuntary smooth muscle bands). Vascular endothelial functions include:

- Absorption of oxygen, nutrients, and essential hormones.
- Maintain local vascular homeostasis.
- Vaso-reactivity and vascular inflammation control through nitric oxide synthesis and bioavailability (c-GMP pathway). Maintaining optimal balance between vascular antioxidants (catalase and super oxide dismutase) and pro-oxidative hormones and reactive oxygen species (endothelin, angiotensin II).
- Local vascular homeostasis (LVH) and coagulopathy through regulation of local hormones (PDGF, VDGF, and anticoagulants such as interleukins, prostaglandins – PGE, PGI, and prostacyclin).
- Protective functions – impermeable barrier to toxins and chemotaxis regulation to prevent vascular inflammation through GAP junction modulation.
- Endothelial integrity, vaso-reactivity, and GAP junction activity are regulated by balanced reflex SNS and PSNS input to the vascular system. This is a centrally regulated process from brainstem CVN (central vagal nucleus).
- Abnormal vaso-reactivity is a function of endothelial dysfunction commonly associated with T2DM.
- ANSD (autonomic nervous system dysfunction) causes systemic vascular inflammation and hypercoagulable state triggering endothelial dysfunction. Increasing evidence for inflammatory etiology for atherosclerosis with inflammatory markers – hsCRP and homocysteine demonstrated in atherosclerosis.
- Several studies have linked T2DM and vaso-reactivity due to endothelial dysfunction. However, recent study (Yong-Jian Li, Seung-Woon Rha – Cardiovascular Center, Korea University, Guro-gu, Seoul, Korea) showed no association of T2DM with CAS (coronary artery spasm), suggesting the existence of a different mechanism for coronary artery spasm and CAD (*J Invasive Cardiol*. 2014;26 (6):234–239).

Dysautonomia is the underlying etiology for T2DM and endothelial dysfunction. Restenosis in diabetic vasculitis is triggered by increased PAI-1 expression and suppression of tPA with more fibrosis and less hyperplasia. Increased pro-inflammatory cytokines (TNF-α, IL-1β) trigger endothelial dysfunction with vascular inflammation and hypercoagulable state. These alterations in LVH are triggered by dysautonomia.



Courtesy: EndotheliX, Inc, VENDYS vascular reactivity measurement.

4. Dysautonomia/T2DM/Atherosclerosis

- Atherosclerosis is initiated by retention of atherogenic lipoprotein particles that trigger maladaptive inflammatory response in the vascular wall.
- Oxidative damage, endothelial dysfunction, and activation of immune responses through interleukins and prostaglandins lead to vascular atherosclerosis.
- Hypercoagulable state is induced that causes acute vascular events.
- These processes are triggered by dysautonomia. Autonomic system regulates vascular wall immune responses and c-GMP pathways that maintain nitric oxide (NO) concentration. NO induces vasodilatation and endothelial stabilization to maintain vaso-reactivity and oxidative free radical concentration.

Auto regulatory system in the body affects all the involuntary and reflex mechanisms in our body.

- Auto regulatory system maintains body homeostasis (fluid and electrolyte balance and temperature regulation) and replenishes the essential physiologic functions and sustains various organ systems – cardiovascular system, hormonal regulation and responses, vascular integrity, liver enzyme regulation (cytochrome P450, etc) metabolism, gastro-intestinal motility, and hormones. Heart beat and breathing are also maintained by CVN through regulating the brainstem cardiovascular and respiratory centers. Sleep cycle is also regulated by this system through complex interactions between brainstem nuclei via CCALA. Properly regulated sleep is an essential physiologic process during which parasympathetic surge maintains sleep cycle – REM and NREM sleep. During sleep cycles parasympathetic stimulation triggers physiologic replenishment of hormones and various organ systems. Dysautonomia results in abnormal sleep regulation and metabolic derangement. Dysautonomia also triggers leptin resistance. Leptin resistance is believed to be the underlying etiology for insulin resistance. Elevated plasma leptin levels and increased human soluble leptin receptor (hsLR) concentrations have been noted in T2DM patients. Hyperleptinemia in turn promotes hyper-sympathetic state and hypercoagulable state by expression of functional leptin receptors on platelets. Hyperleptinemia