Article Section

Role of Incretins in Atherosclerosis

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Abstract

Incretins are ga rointe inal hormones secreted in response to oral glucose intake in a glucose dependent manner. The predominant incretins are glucagon like peptide 1 (GLP1) and glucose dependent insulinotropic polypeptide (GIP). GLP1 is secreted from endocrine L-cells in di al ileum and colon while GIP is secreted from K- cells in duodenum and jejunum. Intere ingly, GLP1 and GIP receptors are widely di ributed in various tissues and organs not only in the pancreas. This indicates extra-pancreatic e ects of these hormones. (1,2)

In diabetes, GIP level is near normal but its function is impaired while on the other hand GLP1 secretion is impaired but it has preserved insulin secretory e ect. Unfortunately, GLP1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV) enzyme. To overcome this rap-id breakdown, incretin-based therapy was developed including incretin mimetics (GLP-1 receptor agoni s) and DPP-IV inhibitors that inhibit the breakdown of GLP-1. (1,2)

Incretins have a pleotropic e ect as they exert multiple functions in various organs through both direct and indirect mechanisms. Their e ect on in ammation and vascular endothelium sugge s their potential role in atherosclerosis. (3,4)

Role of GLP1 and GLP1 receptor agoni s in atherosclerosis: (gure 1)

The direct anti-in ammatory e ect of GLP1 recep-tor agonists is exerted through: Reduction of TNF α mediated expression of platelet activator inhibitor 1 (PAI-1), ICAM-1, and VCAM-1in vascular endo-thelial cells (VECs), limiting lymphocyte recruitment , reducing extracellular matrix remodeling, in-creasing nitric oxide (NO) production and decreas-ing in ammatory chemokine/cytokine production. (Moreover, GLP1 and GLP1 receptor agoni s have an indirect anti-atherosclerotic e ect through their potential glycemic, blood pressure and weight reduction bene ts. They also improve lipid pro le by controlling chylomicron secretion through decreas-ing inte inal lymph ow, reducing triacyl glycerol (TAG) absorption and reducing inte inal produc-tion of apolipoprotein B-48. (5,6)

GLP1 is associated with decrease in carotid intima media thickness (IMT). Additionally, GLP1 receptor agoni s' cardiovascular outcome trials (CVOTs) proved cardiovascular protective e ect of this class of drugs making them the be therapeutic option in patients with type 2 diabetes on metformin therapy and having e ablished cardiovascular disease or of high risk. (7)

Role of GIP in atherosclerosis:

Regarding GIP, its function is impaired in diabetes and udies on its relation to atherosclerosis are limited. GIP e ects of atherosclerosis are con ict-ing. Previous udies concluded an anti-atherosclerotic e ect of GIP while others found a pro-atherosclerotic potential of it. The anti-atherosclerotic e ect of GIP is mediated through AMP-activated protein kinase (AMPK) activation and imulation of NO production in VECs and suppression of foam cell formation and in amma-tory responses in monocytes/macrophages and sup-pression of cell proliferation in VSMCs. (8,9)

On the other hand, evidence sugge ing its pro-atherosclerotic e ect is though imulating VECs production of endothelin-1 (ET-1) which mediates o eoponin production and provokes in ammatory responses in adipocytes. The high level of o eo-ponin has been linked to the presence and extent of coronary artery disease. (8,9) Furthermore, high levels of GIP were associated with increased carot-id IMT. (10)

Recently, GIP/GLP1 receptor co-agoni s proved to have better glycemic and weight control than selective GLP1 receptor agoni s. This gave GIP a therapeutic potential opening the eld for further ud-ies. (4)

Role of DPP-VI inhibitors in atherosclerosis:

Although DPP-VI inhibitors are expected to perform the same action of GLP1 receptor agoni s as they act through inhibiting degradation of endogenous GLP1 prolonging the duration of its action, their e ect on body weight and cardiovascular protection are neutral. This may be explained by the dual mechanism of action of DPP-VI inhibitors through GLP1 dependent and independent e ects. Their GLP1 dependent actions have an anti-atherosclerotic e ect via reduction of reactive oxygen species, up-regulation of adiponectin expres-

sion and decreasing monocyte adhesion to VECs by inhibition of TNF α mediated induction of PAI 1 and adhesion molecule expression. (12)
In contrary, DPP-VI inhibitors' GLP1 independent action arises from the presence of other substrate for DPP-VI enzyme like substance B and stromal cell derived factor 1 (SDF1). The inhibition of this enzyme will raise the serum level of these substrates increasing their effects. Increasing substance B levels will lead to sympathetic activation which will result in vasoconstriction while increasing SDF1 will lead to increase angiogenesis and eventually plaque instability. The end result of the GLP1 independent mechanism of action of DPP-VI inhibitors is enhancing atherosclerosis. (13)
Further udies are required to clarify this con icting data regarding the relation between incretins and ather osclerosis.

Conclusions:

- Incretin Hormones have a pleotropic e ect.
- Clinical trials show favorable e ects of in-cretin-based therapy on cardiovascular out-comes.
- GLP1 receptor agoni s exert direct and indi-rect anti-atherosclerotic e ect.
- GIP has a controversial e ect promoting both anti and pro-atherosclerotic e ect.
- DPP-VI inhibitors' e ects on atherosclerosis are through both GLP1 dependent and inde-pendent mechanisms.

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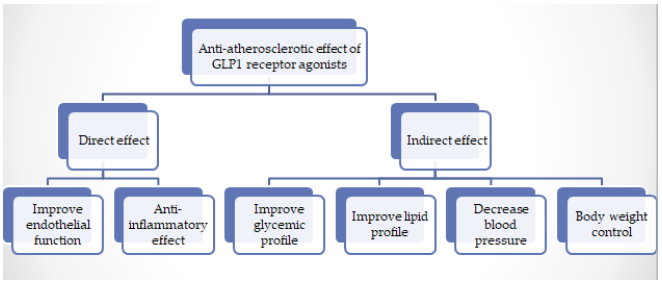

Figure 1: anti-atherosclerotic effect of GLP1 Receptor agonists.

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