Do We Truly Understand the Scope of GPLIs?

Gulfreen Waheed[1], Amina Husnain [2]

[1]Department of Obstetrics & Gynaecology, Avicenna Medical College & Avicenna Hospital, Lahore; [2]Department of Medicine, Avicenna Medical & Dental College, Lahore

Correspondence: Prof. Amina Hussain, Department of Medicine, Avicenna Medical & Dental College Lahore- Pakistan
Email: drahusnain@yahoo.com

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Obesity and increasing diabetes mellitus are the bane of modern affluent society. An understanding of the underlying pathophysiological constraints must be understood well any of us can embark upon treating patients of obesity or DM. Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) were identified in crude form by indirect evidence between 1903 to 1930. The plasma half-life of the drugs prepared based on these findings was extremely short. Between 1995 to 2007 we refined their longer half-life formulations (Liraglutide) which facilitated their usage in the management of type 2 diabetes mellitus (T2DM) and obesity.[1] By 2015 (90hr) long half-life formulations (Dulaglutide, Semaglutide) became available which could be given on weekly basis.[1] By 2019 oral formulations had been given FDA approval for oral formulations (Semaglutide) revolutionizing the usage of the incretin based GLP1 Receptor Agonist. GLP-1 RAs have effects on multiple systems e.g. neuroprotective, anti-inflammatory, reductions in systemic inflammatory markers and effects on immune cell function, contribute to cardiovascular and metabolic benefits. Direct actions of gut include modulation of gut microbiome, preserving pancreatic beta-cell function and potentially promoting beta-cell regeneration[1]. GLP-1 RAs have revolutionized obesity management, demonstrated cardiovascular and renal protection, and have the promise to improve neurodegenerative disorders. Many unexplored applications of this group of medications show promise to further revolutionize prevention of cardiovascular events.[1-4]

Pancreatitis and thyroid tumors got the initial attention as complications, but their fear has largely been attenuated with time.[3] Loss of lean mass and regain of weight after stopping the treatment of obesity are the among the concerns of the day.[1,3] Individualization of usage strategy and treatment regimen for every patient will have to be tailored for each patient. These treatments have not been available to all patients due to a high cost of treatment with GLP-RAs.[3,4] As the industry begins easy availability for the majority, combinations of older treatments can be made with these wonder drugs. Physicians are getting used to safer and more frequent use of GLP-RAs and the medical fraternity has already begun raising hopes for future usage in other indications like metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, knee osteoarthritis, polycystic ovary syndrome, neurodegenerative disease, and substance use disorders.[3,4] One example is the proportionately more loss of lean body mass up to 25% during weight loss usage can be improved with resistance training and increases protein intake before myostatin inhibitors and selective androgen receptor modulators may need to be added. Likewise strategizing the treatment of obesity with the addition of older treatments at the conclusion of GPL-RAs use to prevent rebound weight gain.[3,5,6] We are all learning better use of the drug.

Current discussions at various fora suggest that newer drugs are getting more potent and combinations with other drugs not only increase the efficacy but decrease the undesired side effects also like potential combinations include GLP-1 RAs with SGLT-2 inhibitors (sodium-glucose transport protein-2), amylin analogs, or central nervous system appetite modulators, such as phentermine or bupropion. These wonder drugs have had their own share of attention by the press internationally and recently US government has convinced the industry to reduce the prices so more people could benefit.[4] It has become available now in many brand names in Pakistan as well and more and more patients are using GLP1-RAs.[5,7] Locally very few publications have been produced as yet about Ozempic. There is need to begin research, especially into

the basic or bench research on such products. It is a known fact that Ozempic may not work in 10%of population due to genetic variations which may also be true in our patients.[9] Our pharmaceutical industry should take the initiative and the universities should accept the challenge. Three well reported reviews based on Cochrane data has been criticized just because the funding came from pharmaceutical companies alone.[10] The system of development of research drugs being done in the west and sale in the developing world cannot be expected to reverse until our medical research community doesn't fall vertically in line with the industry. Universities are not producing the research which can be useful to the industry and likewise the industry is running on imported drugs.[8] The gap between the two segments of the society must be patched. Considering the potential of GLP1-RAs more large scale research is required and Pakistan has the workforce and many facilities now for the development of medical research culture. A collaborative effort by the academician and the pharma industry will be most fruitful.

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