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Review Article

Would it be Medically Smart to Offer GLP1 Agonists to Patients Instead of Bariatric Surgery: Looking into the Mirror for Evidence?

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Abstract

By 2030, over 2.16 billion adults globally are projected to be overweight, with 1.12 billion classified as obese. Glucagon-like peptide-1 (GLP-1) receptor agonists have recently shown 15-20% weight loss in adults with obesity, outcomes comparable to those achieved through bariatric surgery. However, meta-analyses of clinical trials indicate bariatric surgery still yields greater reductions in weight and BMI, with similar improvements in glycemic control. Although GLP-1 agonists have gained popularity in treating obesity and metabolic disorders, concerns are emerging regarding adverse effects, including gastrointestinal distress, pancreatitis, and potential neuropsychiatric risks such as depression. In particular, GLP-1 agonists may attenuate dopamine function, raising concerns

for individuals with Reward Deficiency Syndrome (RDS), a genetically influenced condition linked to compulsive eating and addiction. Our laboratory examined genetic and psychosocial data from bariatric surgery patients and found that 76% had high Genetic Addiction Risk Severity (GARS) scores, suggesting hypodopaminergia. Certain gene variants, such as DRD2, DRD4, and OPRM1, correlated with weight loss outcomes and addiction-related traits. Moreover, addiction transfer, where patients replace food addiction with other compulsive behaviors post-surgery, was observed, likely due to shared dopaminergic pathways. These findings support the need for a precision medicine approach. Routine genetic screening may help identify patients at risk of poor outcomes or addiction transfer and guide the judicious use of GLP-1 agonists. Caution is warranted when prescribing these agents to individuals with hypodopaminergic traits.

Keywords: Glp1 Agonists; Weight Loss; Bariatric Surgery; Hypodopaminergia; Adverse Effects; Genetic Testing

Introduction

It is predicted that by 2030, globally, an estimated 2.16 billion adults will be overweight, and 1.12 billion will be obese. Glucagon-like peptide-1 (GLP-1) receptor agonists recently demonstrated 15% to 20% weight loss in adults with obesity, a range which has previously been achieved only with bariatric surgery. However, six studies, encompassing 332 patients, among randomized controlled trials, mean difference in weight between all bariatric surgery types and GLP-1 receptor agonists was -22.68 kg (95% CI: -31.41 to -13.96), mean difference in BMI was -8.18 kg/m^2 (95% CI: -11.59 to -4.77), and mean difference in glycated hemoglobin was -1.28% (95% CI: -1.94% to -0.61%). Among observational studies, the mean difference in weight was -25.11 kg (95% CI: -40.61 to -9.60), and mean difference in BMI was -10.60 kg/m^2 (95% CI: -17.22 to -3.98). Only one observational study reported glycemic outcomes. In adults with obesity, bariatric surgery still confers the highest reductions in weight and BMI but confers similar effects in glycemic control when compared with GLP-1 receptor agonists [1].

Glycogen is the main storage form of glucose in the human body. The liver, skeletal muscle, and to some extent adipose tissue, store glucose as glycogen in the post-prandial state [1]. As there is currently a global epidemic of metabolic syndrome, characterized physiologically by a grouping of symptoms such as abdominal obesity, insulin resistance, and hypertension, there is a need for medical and pharmacological interventions to combat this crisis [2]. GLP-1, an incretin hormone that can modulate several metabolic pathways, has become a popular target for pharmacological intervention in metabolic disorders [3]. The efficacy of GLP-1 agonists is primarily attributed to their neurological effects on appetite suppression, food-seeking behavior, and peripheral effects on gastric emptying and insulin secretion [4]. GLP-1 plays a role in glycogen metabolomics and energy expenditure, however it is not fully understood [5,6].

Type 2 diabetes mellitus (T2DM) is a slow-developing disease that arises from years of insulin resistance and a progressive decline in β-cell function. Early in the disease, β-cells compensate by increasing insulin production, preventing hyperglycemia. however, as the disease progresses, adipose-driven impairment of β-cells worsens, leading to T2DM when approximately 40–60% of β-cell mass is lost [7]. The pathogenesis of T2DM can be explained by the twin cycle hypothesis. The twin cycle hypothesis suggests that long-term excess calorie intake leads to triglyceride accumulation in the liver, impairing insulin function. This hepatic insulin resistance increases gluconeogenesis, leading to elevated glucose and insulin levels [7]. β-cell dysfunction arises from interactions between environmental factors and molecular pathways. Nearly 90% of individuals diagnosed with T2DM have obesity or are overweight, as classified by a body mass index (BMI) greater than or equal to 25 for overweight and 30 for obesity [8]. Obesity has been previously connected to a concept known as Reward Deficiency Syndrome, where individuals with obesity have intrinsic decreased activity of the brain's reward circuitry, leading to hyperphagia of highly- palatable foods that contribute in significant increases in energy intake [9]. Obesity- related hyperglycemia and hyperlipidemia lead

to insulin resistance and chronic inflammation, exposing β-cells to stresses such as inflammation, endoplasmic reticulum stress, oxidative stress, and amyloid stress [10]. Oxidative stress arises due to the excessive production of free radicals, especially reactive oxygen species that severely impact the neutralizing capacity of intracellular antioxidants. Oxidative stress applies its destructive effects by causing damage to deoxyribonucleic acid (DNA), proteins, and lipids [11]. In individuals with obesity, adipose tissue becomes a source of inflammation, producing higher levels of proinflammatory markers like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemotactic protein-1 [12]. This inflammatory state contributes to insulin resistance and provokes β-cell dysfunction in the pancreas.

An important marker of adipose tissue health is plasma adiponectin, which is associated with insulin sensitivity. Adiponectin levels are low in obesity. In the liver, adiponectin decreases the influx of fatty acids and increases fatty acid oxidation. Adiponectin serves as a reliable marker for insulin sensitivity, with its levels inversely correlating with the degree of insulin resistance and metabolic dysfunction.

Understanding these basic facts provides evidence for the role and potential benefits of GLP1 agonists regarding T2DM and obesity in general. However, we must carefully consider a degree of evidence against the overprescribing of GLP1 agonists as the new "wonder" drug for these conditions. However, a long list of adverse effects continues to become evident with these drugs including lactose intolerance [13]; gastrointestinal [14]; induced autoimmune hepatitis. [15]; negative impact on the retina [16]; severe acute pancreatitis leading to death after four years of GLP-1RA use[17]; serious adverse drug events [18]; increase the risk of ketosis [19]: risk for medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 [20]; induced granulomatous panniculitis [21]: elevated risk of incident bone fractures [22] ; regaining weight [23]; accelerated breast cancer progress [24]; central GABA (gamma-aminobutyric acid) release and reduced dopamine function [25]; cardiac function deterioration [26]: induced polyarthritis [27]; positively associated with 221 immune cell phenotypes [28]; hypoglycemic episodes [29]; tumor promoting effects [30]; risk of incident glaucoma [31]; in patients with heart failure with reduced ejection fraction (HFrEF) increased risk for arrhythmia; heart failure hospitalizations and heart failure [32]; Hemiplegic Migraines [33]**;** depression/suicidal ideation [34-36].

In spite of these negative reports there is indeed a plethora of positive benefits credited to GLP1 agonists that continue to significantly offer real benefits to victims of reward deficiency and associated addictive behaviors [37-50]. However, the purpose of this editorial is to provide a cautionary note to the field of bariatric medicine particularly surgery. It is indeed critical to consider both the neurogenetic trait and epigenetic state linking its established induction of dopaminergic attenuation with potential of worsening clinical outcome especially in carriers of DNA and epigenetic "hypodopaminergic antecedents (Table 1).

To this end it is particularly important to point out recent published genetic results primarily from our laboratory involving bariatric surgical clinical outcomes. Now after many years of successful bariatric (weight-loss) surgeries directed at the obesity epidemic clinicians are reporting that some patients are replacing compulsive overeating with newly acquired compulsive disorders such as alcoholism, gambling, drugs, and other addictions like compulsive shopping and exercise. Evidence from psychiatric genetic animal and human studies that link compulsive overeating, and other compulsive disorders, helps to explain the phenomenon of addiction transfer [51].

Possibly due to neurochemical similarities, overeating and obesity may act as protective factors reducing drug reward and addictive behaviors. In animal models of addiction withdrawal from sugar induces imbalances in the neurotransmitters, acetylcholine and dopamine, similar to opiate withdrawal [52] Many human neuroimaging studies have supported the concept of linking food craving to drug craving behavior [53]. Previously our laboratory coined the term Reward Deficiency Syndrome (RDS) for common genetic determinants in predicting addictive disorders and reported that the predictive value for future RDS behaviors in subjects carrying the DRD2 Taq A1 allele was 74% [54].

While poly genes play a role in RDS, we have also inferred that disruptions in dopamine function may predispose certain individu-

A sample of physicians ' mixed response to glp1 agonists
"Of course there will. GLP-1's are a multibillion dollar issue and millions are flocking to them. However, results are not great in the long term. Also, the =very obese patients for bariatric surgery will see little improvement with GLP1" - Dermatology and Sexual Health Canada
"Personally, I do not like the GLP1s (personal principle) but I suppose that if they do help patients, then there is nothing wrong with bariatric surgery becoming a thing of the past. I have nothing against bariatric surgeons, but I would assume that the costs of management of obesity will go down with the increased use of GLP1"s. Oncology Australia
"When you compare the cost and safety and logistics of what a tablet will be a day against those of major anesthesia including Trendelenberg and laparosocpy lets really hope so. GLP1 agonists are merely the first of a number of pharmaceutical interventions for obesity and although they may never be perfect and need lifelong administration, we must not underestimate the benefits. The US saw the first drop in obesity in 2023, and we have the possibility to massively reduce the need for Cath labs, joint replacements, diabetic care and ITU. We may even be able to afford universal healthcare in the 2050s. Surgery can never be provided on the scale needed to resolve the obesity epidemic that is at the heart of the universal healthcare crisis". General Medicine-Unted Kingdom
As I understand, once the injections are stopped, the Metabolic Syndrome, pre-diabetes, will return. Unless the shots are as cheap as aspirin or generic cough meds, users will need to use injections perhaps for life. A gastric band or bypass will last much longer. One of my Ohio State Univ. College of Medicine, 1959, Dr Douglas Hess, became a general surgeon, went back to his hometown near Bowling Green. There were so many obese people he became a pioneer in GI tract alterations. A recent article in JAMA has suggested that due to the epidemic of obesity in Black and Hispanic school girls, it would be cheaper to do GI by-pass or banding on them all than to spend billions on complications, toxemia, hypertension, diabetes, osteoarthritis, heart disease. Ophthalmology, Aerospace Medicine USA
"There are safer and better ways to get people to lose weight without anatomically modifying their GI tract". Family Medcine -USA
"Bariatric surgery is a very mutilative procedure (except the placement of a ring). The future will be a medical treatment, and the GLP-1 are only the beginning of it " .Research Fellow Belgium
"The drug and food companies seem to only want profit and not solution. Am I alone? Feels like it. Until and unless you improve nutrition……..I believe the phrase is, on a hiding to nothing. Surgery may help. Drugs may help. But until you change mind-sets the money will go on rolling in" General Medicine -United Kingdom
While for many of my patients GLP1-agonists showed significant weight loss, unfortunately there is also significant weight gain, however, unlike many of my associates I carefully review each patient's family history of depression and suicidal ideation prior to prescribing these agents. I look forward to future Genetic testing to help determine dopaminergic trait status. Family Medicne- USA

Table 1: A sample of physicians ' mixed response to glp1 agonists.

als to addictive behaviors and obesity [55]. It is now known that the family history of alcoholism is a significant obesity risk factor. Therefore, we hypothesize here that RDS is the root cause of substituting food addiction for other dependencies and potentially explains this recently described Phenomenon (addiction transfer) common after bariatric surgery [56-64].

Our first study examined genetic data regarding Reward Deficiency Syndrome (RDS) to evaluate their usefulness in counselling patients undergoing bariatric surgery and gathered preliminary data on the potential use in predicting short term (6-month) weight loss outcomes. Patients undergoing bariatric surgery (n = 34) were examined for Genetic Addiction Risk Severity (GARS) [measures the presence of risk alleles associated with RDS]; as well as their psychosocial traits (questionnaires). BMI changes and sociodemographic data were abstracted from Electronic Health Records. Subjects showed ΔBMI (M = 10.0 ± 1.05 kg/m^2) and a mean % excess weight loss (56 ± 13.8%). In addition, 76% of subjects had GARS scores above seven. The homozygote risk alleles for *MAO* (rs768062321) and *DRD1* (rs4532) showed a 38% and 47% prevalence among the subjects. Of the 11 risk alleles identified by

GARS, the *DRD4* risk allele (rs1800955), was significantly correlated with change in weight and BMI six months post-surgery. We identified correlations with individual risk alleles and psychosocial trait scores. The *COMT* risk allele (rs4680) showed a negative correlation with EEI scores (r = -0.4983, $p < 0.05$) and PSQI scores (r = -0.5482, $p < 0.05$). The *GABRB3* risk allele (rs764926719) correlated positively with EEI (r = 0.6161, $p < 0.01$) and FCQ scores (r = 0.6373, $p < 0.01$). The *OPRM1* risk allele showed a positive correlation with the DERS score (r = 0.5228, $p < 0.05$). We also identified correlations between DERS and BMI change (r = 0.61; $p < 0.01$). These data support the potential benefit of a personalized medicinal approach inclusive of genetic testing and psychosocial trait questionnaires when counselling patients with obesity considering bariatric surgery [65]. Future research will explore epigenetic factors that contribute to outcomes of bariatric surgery.

Moreover, in one year follow -up study in the same patients, we found interesting additional results [66]. This study analyzed genetic risk assessments in patients undergoing bariatric surgery to serve as a predictive factor for weight loss parameters 1 year after the operation. Thirty (30) patients were assessed for Genetic Addiction Risk Severity (GARS), which analyzes neurogenetic polymorphisms involved in addiction and reward deficiency. Genetic and psychosocial data collected before the operation were correlated with weight loss data, including changes in weight, body mass index (BMI), and percentage of expected weight loss (%EWL). Results examined correlations between individual gene risk alleles, 1-year body weight data, and psychosocial trait scores. Spearman's correlations revealed that the *OPRM1* (rs1799971) gene polymorphism had significant negative correlation with 1-year weight (r_s = -0.4477, $p < 0.01$) and BMI (r_s = -0.4477, $p < 0.05$). In addition, the *DRD2* risk allele (rs1800497) was correlated negatively with BMI at 1 year (r_s = -0.4927, $p < 0.05$), indicating that one risk allele copy was associated with lower BMI. However, this allele was positively correlated with both ΔWeight (r_s = 0.4077, $p < 0.05$) and %EWL (r_s = 0.5521, $p < 0.05$) at 1 year post-surgery. Moreover, the overall GARS score was correlated with %EWL (r_s = 0.4236, $p < 0.05$), ΔWeight (r_s = 0.3971, $p < 0.05$) and ΔBMI (r_s = 0.3778, $p < 0.05$). Lastly, Food Cravings Questionnaire (FCQ) scores were negatively correlated with %EWL (r_s = -0.4320, $p < 0.05$) and ΔWeight at 1 year post-surgery (r_s = -0.4294, $p < 0.05$). This suggests that individuals with a higher genetic addiction risk are more responsive to weight loss treatment, especially in the case of the *DRD2* polymorphism. Indeed, these findings are not surprising because Noble., *et al.* [67] found similar findings in an alcoholic cohort. Various types of alcoholics have been described and heredity has been shown to be involved in some of these types. An important role of the mesolimbic dopamine system has been suggested in the reinforcing effects of alcohol and recent molecular genetic studies are implicating the gene for the D2 dopamine receptor (DRD2) in alcoholism. In a double-blind study, bromocriptine, a DRD2 agonist, or placebo was administered to alcoholics with either the A1 (A1/A1 and A1/A2 genotypes) or only the A2 (A2/A2 genotype) allele of the DRD2 gene. The greatest improvement in craving and anxiety occurred in the bromocriptine-treated A1 alcoholics and attrition was highest in the placebo-treated A1 alcoholics. The feasibility of a pharmacogenetic approach in treating certain types of alcoholics is suggested [67]. These results should be translated clinically to improve positivity and attitude related to weight management by those individuals born with the risk alleles (rs1800497; rs1799971).

Policy implications and future directions

The dramatic rise in the use of GLP-1 receptor agonists (GLP-1RAs) for obesity and type 2 diabetes treatment represents both a therapeutic milestone and a potential blind spot in precision medicine. While these agents offer weight loss comparable to bariatric surgery in selected populations, their broad application risks overlooking vulnerable subgroups-particularly individuals with hypodopaminergic traits as identified through Genetic Addiction Risk Severity (GARS) testing and associated behavioral screening tools [68-70].

Our findings suggest that up to 76% of bariatric surgery candidates exhibit elevated GARS scores, a surrogate for underlying Reward Deficiency Syndrome (RDS), which is linked to increased susceptibility to addiction transfer, compulsive behavior, and dopaminergic dysregulation [71]. Emerging evidence also highlights potential neuropsychiatric side effects of GLP-1RAs, including depression, reduced dopamine signaling, and suicidal ideation in rare cases [72]. These concerns underscore a critical policy gap: there is no current requirement for genetic or psychosocial screening before initiating GLP-1 therapy or referring for surgical intervention.

To address this, we propose the following policy framework

- **Launch of a CMS innovation center pilot program:** A prospective demonstration project should evaluate the utility and cost-effectiveness of integrating GARS testing and behavioral screening into the treatment pathway for patients with obesity. Stratifying patients based on dopaminergic risk phenotype may improve long-term outcomes and reduce iatrogenic harm [73].
- **Development of a clinical decision support algorithm:** A standardized GLP-1 Risk Stratification Algorithm (GRSA) should be created for use in electronic health record systems. This tool would incorporate GARS scores, psychological risk inventories (e.g., DERS, FCQ), and family history of addiction to guide decisions between pharmacologic and surgical management [74].
- **FDA labeling and risk acknowledgment:** We recommend that the FDA consider updating the product labels of GLP-1RAs to include cautionary guidance for use in individuals with known hypodopaminergic profiles or history of addictive behaviors. Similar pharmacogenomic considerations have been incorporated in other drug classes, including antipsychotics and antidepressants [75].
- **Coverage expansion for genetic screening:** Private and public insurers should be encouraged to reimburse GARS testing as part of comprehensive obesity treatment planning, paralleling reimbursement practices for other precision-based tools such as BRCA testing in oncology or pharmacogenomic panels in psychiatry [76].
- **Ethical Safeguards and Equity Considerations:** Institutions implementing GARS-guided care must develop transparent, consent-based protocols to protect against genetic discrimination and ensure equitable access. Particular attention must be paid to avoiding racial or socioeconomic exclusion from personalized obesity care [77].
- **Provider Education and Training:** A federally supported CME curriculum should be developed to educate primary care providers, endocrinologists, and bariatric surgeons on the implications of neurogenetic risk, the safe use of GLP-1RAs, and best practices for shared decision-making with at-risk patients [78-91].

Conclusion

Having a direct message related to the cautionary note concerning the administration of GLP1 agonists to severely obese patients potentially strong candidates for bariatric surgery, we found 76% of subjects had GARS scores above seven indicating hypodopaminergia. This finding may be quite critical in terms of blindly prescribing GLP1 agonists, that modify or even attenuate dopaminergic function, potentially worsening the hypodopaminergic trait (DNA) as well as potential further insults from the environment(epigenetic).

As the GLP-1 class reshapes the therapeutic landscape for obesity, its promise must be matched by precision, caution, and ethical responsibility. A neurogenetically informed framework offers a practical and scientifically grounded path forward-one that acknowledges the heterogeneity of obesity and the neurobiological individuality of those we treat.

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Author Contribution

The initial draft was developed by KB. The second draft was further developed by KUL and MP. The rephrasing was performed by ALP. All the co-authors reviewed ,provided edits and approved the final draft.

Conflict of Interest

KB via his companies owns IP and patents both domestic and foreign patents both issued and pending related to gars and KB220.

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