DISCOVERY AND DEVELOPMENT OF SEMAGLUTIDE AS ANTI-OBESITY MEDICATION TO REDUCE CARDIOVASCULAR RISK IN DIABETIC PATIENTS

Abstract

Obesity and type 2 diabetes (T2D) are major global health concerns, with rising prevalence over the world. Both conditions pose substantial cardiovascular disease (CVD) riskand cardiometabolic complications. Traditional glycaemic control in T2D has been challenging, leading to glucagon-like peptide-1 receptor agonist (GLP-1RA) development like semaglutide. Semaglutide, with its longer half-life, offers administration on a weekly basis and has shown efficacy in reducing weight and CVD risk. Semaglutide enhances the action of incretin via stimulating GLP-1 receptors, leading to increased insulin secretion, decreased hepatic gluconeogenesis and decreased glucagon release. It also promotes weight loss through decreased energy intake and delayed gastric motility. Obesity and T2D have adverse effects on the immune and thromboembolic systems, increasing the risk of infections and CVD. Weight reduction can significantly improve metabolic function and reduce diabetes comorbidities. Semaglutide, with its favorable pharmacokinetics and efficacy, provides a valuable treatment option in managing obesity and reducing cardiovascular risk in diabetic patients. However, it is essential to consider potential adverse effects and individual patient factors when prescribing semaglutide for optimal outcomes.

Keywords: Semaglutide, Obesity, Cardiovascular Disease, Type 2 Diabetes

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I. INTRODUCTION

Obesity stands as a significant global healthcare challenge, impacting over 600 million adults worldwide. It is characterized by the accumulation of excess adipose tissue, posing significant health risks. This condition, marked by a chronic, relapsing course, has seen a substantial increase in its prevalence over the past few decades, and this pattern is going to continue. While the global prevalence of obesity is at 13%, numerous nations experience even higher rates. For instance, the prevalence of adult obesity surged from 31% to 42% between 1999-2000 and 2017-2018 in the United States. Similarly, over a decade leading up to 2017, European countries witnessed an escalation from 10% to 40% in obesity rates. [1-7].

Obese people are more likely to suffer from cardiovascular disease (CVD) and its consequences, including type 2 diabetes (T2D)(8). Diabetes-related cardiovascular disease (CVD) is the leading cause of mortality.(9). Obesity is also linked to poor outcomes after illnesses like the flu and SARS-CoV-2. [8-11].

When managing obesity to reduce cardiovascular risk in diabetic patients, a comprehensive treatment approach is necessary to address two conditions simultaneously. This approach should focus on lifestyle modifications and Pharmacological treatments to achieve optimal outcomes. Guidelines recommend lifestyle modification as the primary treatment for overweight or obesity, but the achieved weight loss is usually modest and often regained later [12-18].

Earlier medications for maintaining a healthy weight, include orlistat, phentermine-to piramate, and naltrexone-bupropion. Liraglutide 3.0 mg once daily subcutaneous injection was the first GLP-1 receptor agonist (GLP-1RA) to get weight-management approval. Pharmacological therapies for obesity are an important complement to lifestyle changes, but up until recently, the agents on the market only provided modest weight reduction gains above those made by lifestyle changes. The effectiveness of the novel anti-obesity drug semaglutide in lowering weight and the risk of CVD has been demonstrated. Semaglutide is a powerful long-acting substitute of the glucagon-like peptide-1 (GLP-1) that has been shown to reduce caloric intake, decrease appetite, and promote feelings of fullness and contentment. This impact has been demonstrated to result from central nervous system GLP-1 receptor activation, with additional indirect modulation of neuronal activity related to appetite regulation, food intake, and food choice. [7].

II. DISCOVERY AND DEVELOPMENT OF SEMAGLUTIDE

Glycemic management has always been the main aim in the therapy of type 2 diabetes mellitus, although multiple therapies including optimizing hyperglycemia, obesity, hypertension, dyslipidaemia, and cardiovascular variables are both important. Despite a broad range of treatment choices, it is still very difficult to keep blood sugar levels steady in a clinical context without suffering negative effects like hypoglycemia episodes. Hope for successful diabetes control is provided by the development of recombinant human proteins and glucagon-like peptide-1 (GLP-1) receptor agonists [19-23].

GLP-1 is an essential incretin hormone that exerts its effects through a range of mechanisms, including increased insulin secretion and decreased hepatic gluconeogenesis based on glucose levels, and restricting the release of glucagon. Furthermore, it induces delayed gastric emptying, leading to decreased appetite and energy intake. Its particular significance lies in treating individuals with obese type 2 diabetes, as it not only lowers HbA1c levels but also aids in weight loss, all without the risk of hypoglycemia. However, due to degradation mediated by Dipeptidyl Peptidase-4 (DPP-4) and Neutral Endopeptidase, its short half-life (1-2 minutes) impairs its therapeutic effectiveness. To get beyond this obstacle, alternative agonists of the GLP-1 receptor like semaglutide, dulaglutide, and liraglutide have been developed. These analogues are designed to mimic GLP-1's actions but are less susceptible to breakdown by proteolysis. Notably, therapies based on exendin (e.g., exenatide, lixisenatide) and analogues of GLP-1(e.g., semaglutide, liraglutide, dulaglutide) have been successfully employed in clinical practice.[21,24-30].

Semaglutide, the first oral GLP-1 receptor agonistis currently marketed in subcutaneous and oral dosage forms. It was first authorized as a type 2 diabetes second-line treatment to help with glycemic control, but it is additionally being investigated for use as an anti-obesity drug. In those who have at least one weight-related comorbidity in addition to obesity or overweight, semaglutide was tested as a subcutaneous treatment once per week for weight control in the STEP Phase 3a clinical research programme. [31-32].

III. UNDERSTANDING SEMAGLUTIDE

The development of semaglutide was based on the extensive amount of research that occurred during the development of liraglutide. Semaglutide has a half-life that is much longer than that of liraglutide, enabling once-weekly dosage as opposed to once daily. The injectable approach may be a barrier for some potential users, even though there have been noticeable gains over once or twice daily subcutaneous doses. Sodium N-[8-(2-hydroxybenzoyl) amino]caprylate, also known as SNAC, is an enhancer of absorption that has been demonstrated to provide therapeutic amounts of semaglutide when paired with the later. Semaglutide is protected from proteolytic breakdown in the stomach and is promoted to be absorbed through the gastric mucosa thanks to SNAC's brief effects on transcellular pathways. Comparatively, oral, and subcutaneous semaglutide demonstrated similar glycemic and weight responses when exposed to equivalent doses [33-35].

1. **Pharmacokinetics of Semaglutide:** Table 1 represents the comparative analysis of pharmacokinetic parameters between subcutaneous (s.c.) and oral semaglutide [31].

Table 1: Pharmacokinetics of Semaglutide

Characteristics	Semaglutide (subcutaneous injection)	Semaglutide (oral)
Absorption	89%	0.4-1%
Absolute bioavailability	65 ng/ml (0.5 mg once a week)	6.7 nmol/L (7 mg once per day)
Steady state plasma conc.	123 ng/ml (1 mg once a week)	14.6 nmol/L (14 mg once per day)

Time required to reach steady state concentration	4-5 weeks	4-5 weeks
Time required to achieve maximum concentration	1–3 days	1 hour
Distribution		
Volume of distribution	12.5 liters	8 liters
Protein binding	greater than 99%	greater than 99%
Metabolic pathway	Fatty acid oxidation develops after proteolytic breakdown	Fatty acid oxidation develops after proteolytic breakdown
Elimination profile		
Elimination $t_{1/2}$	01 week	01 week
Rate of clearance	0.05 litres/ hour	0.04litres/ hour

2. **Mechanism of Semaglutide:** Semaglutide stimulates GLP-1 receptors to improve incretin function, leading to several mechanisms like glucose-dependent insulin secretion, decreased hepatic gluconeogenesis and suppression of glucagon release. As a result, fasting and postprandial glucose levels are reduced. It also improves β-cell functioning and increases insulin production, as indicated by abeneficial proinsulin to insulin ratio. Furthermore, improved insulin sensitivity is observed, likely due to overall body weight reduction. Semaglutide also promotes weight loss through decreased energy intake and delayed gastric motility [36-40].

3. **Semaglutide Indications:** As per the recommendation of American Diabetes Association 2020, the indications for Semaglutide are listed in Table 2 [31].

Table 2: Indications for Semaglutide (As per American Diabetes Association 2020)

Parameters	Indication
Efficacy	High
Cost	High
Oral/Injectable	Both available
Weight loss	Yes
Risk of Hypoglycaemia	No, Semaglutide monotherapy
	Yes, the dose has to be decreased when used along with insulin or other hypoglycemic drugs..
Cardiovascular risk	lowers the risk of heart disease
Geriatrics, renal, and hepatic impairment require dosage adjustments	Not necessary
preferred situations	improved glycemic control is necessary.
	To lower HbA1c, injectable treatment is required.

	Switching from injectable to oral treatment is necessary
	Whenever possible, prefer to insulin
	renal impairment and atherosclerotic-related cardiovascular disorders
	Inability to tolerate SGLT-2 inhibitors
	It's essential to lose weight.
Precautions	Avoid in- Multiple Endocrine Neoplasia Syndrome type 2, Pancreatitis, Thyroid Medullary Carcinoma, Progressive Retinopathy, and Congestive Heart Failure (According to EMA)

4. **Adverse Effects of Semaglutide:** Adverse effects associate with Semaglutide are hypoglycemia, gastrointestinal effects (nausea, vomiting and diarrhea), pancreatitis and pancreatic cancer, cardiovascular disease, thyroid cancer, gallbladder cholelithiasis, acute kidney injury, diabetic retinopathy and allergic reactions [41].

5. **Obesity, Diabetes, and Cardiovascular Risk:** People with diabetes and obesity generally have an increased risk of infections, including influenza, and of secondary bacterial infections, and the risk increases with increasing levels of glycated hemoglobin (HbA1C). The immunological response to viral infections is lowered and the risk of subsequent bacterial infections in the lungs is increased even in the short term when blood glucose levels are raised. The "cytokine storm" and abnormal lymphocyte, neutrophil, and macrophage responses reported in the sickest COVID-19 patients may be explained by an immune system that is dysregulated in patients with diabetes and obesity. Obese insulin-resistant individuals have disturbances in the thromboembolic system characterized by endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, and increased amounts of plasminogen activator inhibitor 1, which has a prothrombotic effect. Obesity frequently has a correlation with metabolic syndrome, also known as glucose intolerance, insulin resistance, dyslipidemia, and hypertension. There are similarities between the abnormalities seen in metabolic syndrome and polycystic ovary syndrome (PCOS), leading to the hypothesis that both conditions may share a common pathogenesis involving hyperinsulinemia and glucose intolerance. When body fat builds up excessively, it can cause several metabolic disorders and illnesses, including insulin resistance, atherogenic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), -cell dysfunction, prediabetes, and type 2 diabetes. Type 2 diabetes risk gradually rises along with body mass index (BMI), a measure of obesity. [42-49].

Obese people who have a higher concentration of upper body fat, such as abdominal subcutaneous and intra-abdominal fat, intrahepatic triglycerides, intramyocellular lipids, and pancreatic fat are more likely to develop type 2 diabetes than people who have a lower concentration of body fat (gluteofemoral). It's interesting to note that higher gluteofemoral body fat mass is linked to positive outcomes including enhanced oral glucose tolerance and insulin sensitivity, lower fasting blood sugar and insulin levels, higher HDL cholesterol concentrations, lower plasma triglyceride levels,

and increased HDL cholesterol concentrations. According to this relationship, which holds true for lean, overweight, and obese people alike, having greater gluteofemoral fat may offer protection against type 2 diabetes regardless of weight. Insulin resistance that affects several organs and a reduction in insulin production from beta cells are the causes of type 2 diabetes. Because obesity affects both insulin function and beta cell performance, it is a primary factor in the growth in type 2 diabetes incidence worldwide. [50, 51].

Obesity results in elevated levels of free fatty acids (FFAs) that are released into the bloodstream and distributed throughout the body. The conventional belief that increased plasma FFA concentrations play a major role in inducing insulin resistance in the liver and muscles of obese individuals has been widely accepted. Nevertheless, this viewpoint has faced challenges due to conflicting findings across studies and uncertainties about how results from controlled experimental interventions translate to real-world scenarios. In resting conditions among obese individuals, the rate at which free fatty acids (FFAs) are released into the bloodstream is comparatively lower than in lean individuals, considering their body fat mass. However, due to the substantial overall body fat content, the relative rate of FFAs released in relation to body fat-free mass is higher in those with obesity compared to their lean counterparts. Both obesity and type 2 diabetes negatively impact the metabolism of lipids within the liver, promoting in the emergence of nonalcoholic fatty liver disease (NAFLD). This condition affects approximately two thirds of the population with type 2 diabetes or obesity. The buildup of fat in the liver primarily results from increased triglyceride production rather than a reduction in fatty acid oxidation or impaired triglyceride export by the release of very low density lipoprotein (VLDL).Insulin resistance and chronic hyperinsulinemia lead to heightened hepatic de novo lipogenesis, which is the process of synthesizing fatty acids from glucose. This is accompanied by an augmented delivery of lipogenic substrates to the liver, including glucose and fatty acids derived from the breakdown of triglycerides in adipose tissues (both subcutaneous and intra-peritoneal), as well as from thePlasma triglyceride hydrolysis. Additionally, fatty acids released during the chylomicrons' postprandial lipolysis of triglycerides contribute to this phenomenon. Significantly, weight loss can yield substantial therapeutic benefits by positively affecting metabolic function, type 2 diabetes management, and associated comorbidities. [52-62].

Circulating endothelial cells (CECs) are seen in greater quantities in conditions like T2DM that cause severe vascular damage. The development of atherosclerotic plaques and lesions is facilitated by Risk factors for T2DM include dyslipidemia, hyperglycemia, and hyperinsulinemia as well as other conditions (such insufficient exercise, smoking, and high blood pressure). Dyslipidemia is regarded as a major risk factor for developing CVD in diabetes patients due to increased flow of FFA from insulin-resistant tissues and spillover from entrance into adipocytes. The reason for this is that dyslipidemia encourages inflammatory response, endothelial dysfunction, and platelet hyperactivation. The risk of myocardial infarction (MI), stroke, and peripheral artery disease (PAD) is increased by macroangiopathies because they cause atherosclerosis in the coronary, carotid, and peripheral arteries. One of the main causes of death and morbidity in diabetes patients is thought to be macrovascular problems carried due to EC dysfunction. [63-67].

IV. CONCLUSION

Obesity is a significant global health concern, affecting millions of adults worldwide and increasing the risk of various chronic diseases, including cardiovascular disease (CVD) and type 2 diabetes (T2D). Managing obesity in diabetic patients is crucial for reducing cardiovascular risk, and a comprehensive approach involving lifestyle modifications and pharmacological treatments is necessary.GLP-1 receptor agonist semaglutide, has emerged as a promising anti-obesity medication with potential benefits for reducing cardiovascular risk in diabetic patients. Its mechanism of action includes enhanced insulin secretion, inhibition of glucagon release, suppressed hepatic gluconeogenesis, and reduced appetite and energy intake. Semaglutide has shown efficacy in weight management, making it a valuable treatment option for individuals with obesity and overweight. The pharmacokinetics of semaglutide, whether administered subcutaneously or orally, provides flexibility and convenience for patients. While there are adverse effects associated with semaglutide, its potential benefits in reducing cardiovascular risk outweigh the risks, especially when used in carefully selected patient populations.

Obesity and diabetes are closely interlinked, and their combined presence increases the risk of infections and cardiovascular complications. Addressing these conditions through weight management and improved glycemic control can positively impact overall health and reduce the risk of complications. Weight loss has a profound impact on metabolic function and comorbidities associated with diabetes, including dyslipidemia and insulin resistance. Furthermore, weight loss can alleviate the burden on the cardiovascular system, reducing the risk of atherosclerosis and related macrovascular complications.

In summary, semaglutide shows promise as an effective anti-obesity medication with potential benefits for reducing cardiovascular risk in diabetic patients. Combined with lifestyle modifications, semaglutide can be a valuable tool in managing obesity and diabetes and improving overall health outcomes. However, it is essential to consider individual patient characteristics and medical history when prescribing this medication. Further research and clinical trials are warranted to explore the long-term safety and efficacy of semaglutide in reducing cardiovascular risk in diabetic patients. Ultimately, a multidisciplinary approach involving healthcare professionals and patients' active participation is crucial in the successful management of obesity and diabetes to mitigate cardiovascular risk and improve patient outcomes

REFERENCES

[1] Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. The Lancet. 2016 Apr;387(10026):1377–96.

[2] Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, Després JP, Matsuzawa Y, Loos RJF, et al. Obesity. Nat Rev Dis Primers. 2017 Jun 15;3(1):17034.

[3] Bessesen DH, Van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. Lancet Diabetes Endocrinol. 2018 Mar;6(3):237–48.

[4] Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obesity Reviews. 2017 Jul;18(7):715–23.

[5] Agha M, Agha R. The rising prevalence of obesity: part A: impact on public health. Int J Surg Oncol (N Y). 2017 Jun 22;2(7):17.

[6] Janssen F, Bardoutsos A, Vidra N. Obesity Prevalence in the Long-Term Future in 18 European Countries and in the USA. Obes Facts. 2020;13(5):514–27.

[7]   Bergmann NC, Davies MJ, Lingvay I, Knop FK. Semaglutide for the treatment of overweight and obesity: A review. Diabetes Obes Metab. 2023 Jan 18;25(1):18–35.

[8]   Kosiborod MN, Bhatta M, Davies M, Deanfield JE, Garvey WT, Khalid U, et al. Semaglutide improves cardiometabolic risk factors in adults with overweight or obesity: STEP1 and 4 exploratory analyses. Diabetes Obes Metab. 2023 Feb 28;25(2):468–78.

[9]   Martin-Timon I. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World J Diabetes. 2014;5(4):444.

[10] Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes. 2012 Aug 25;36(8):1072–7.

[11] Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, et al. Individuals with obesity and COVID- 19: A global perspective on the epidemiology and biological relationships. Obesity Reviews. 2020 Nov 26;21(11).

[12] Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocrine Practice. 2016 Jul;22:1–203.

[13] Durrer Schutz D, Busetto L, Dicker D, Farpour-Lambert N, Pryke R, Toplak H, et al. European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. Obes Facts. 2019;12(1):40–66.

[14] Timothy Garvey W. and Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines, AACE/ACE Guidelines, American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity, 2016.

[15] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for Obesity Management in Adults. Obes Facts. 2015;8(6):402–24.

[16] Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. American Psychologist. 2020 Feb;75(2):235–51.

[17] Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity. 2020 Jun 22;28(6):1050–61.

[18] Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-Term Persistence of Hormonal Adaptations to Weight Loss. New England Journal of Medicine. 2011 Oct 27;365(17):1597–604.

[19] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive type 2 Diabetes Management Algorithm – 2017 Executive Summary. Endocrine Practice. 2017 Feb;23(2):207–38.

[20] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 Jan 1;38(1):140–9.

[21] Goldenberg RM, Steen O. Semaglutide: Review and Place in Therapy for Adults With Type 2 Diabetes. Can J Diabetes. 2019 Mar;43(2):136–45.

[22] Astrup A, Finer N. Redefining Type 2 diabetes: "Diabesity" or "Obesity Dependent Diabetes Mellitus"? Obesity Reviews. 2000 Oct;1(2):57–9.

[23] Mauricio D, Meneghini L, Seufert J, Liao L, Wang H, Tong L, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. Diabetes Obes Metab. 2017 Aug;19(8):1155–64.

[24] Tasyurek HM, Altunbas HA, Balci MK, Sanlioglu S. Incretins: Their physiology and application in the treatment of diabetes mellitus. Diabetes Metab Res Rev. 2014 Jul;30(5):354–71.

[25] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet. 2006 Nov;368(9548):1696–705.

[26] Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;8(12):728–42.

[27] Knop FK, Bronden A, Vilsboll T. Exenatide: pharmacokinetics, clinical use, and future directions. Expert Opin Pharmacother. 2017 Apr 13;18(6):555–71.

[28] Leon N, LaCoursiere R, Yarosh D, Patel RS. Lixisenatide (Adlyxin): A Once-Daily Incretin Mimetic Injection for Type-2 Diabetes. P T. 2017 Nov;42(11):676–711.

[29] Buse JB, Nauck M, Forst T, Sheu WHH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. The Lancet. 2013 Jan;381(9861):117–24.

[30] Smith LL, Mosley JF, Parke C, Brown J, Barris LS, Phan LD. Dulaglutide (Trulicity): The Third Once-Weekly GLP-1 Agonist. P T. 2016 Jun;41(6):357–60.

[31] Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev Endocr Metab Disord. 2022 Jun 7;23(3):521–39.

[32] Jensterle M, Rizzo M, Janez A. Semaglutide in Obesity: Unmet Needs in Men. Diabetes Therapy. 2023 Mar 7;14(3):461–5.

[33] Knudsen LB, Lau J. The Discovery and Development of Liraglutide and Semaglutide. Front Endocrinol (Lausanne). 2019 Apr 12;10.

[34] Buckley ST, Baekdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Ronne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018 Nov 14;10(467).

[35] 55th EASD Annual Meeting of the European Association for the Study of Diabetes. Diabetologia. 2019 Sep 5;62(S1):1–600.

[36] Knudsen LB, Lau J. The Discovery and Development of Liraglutide and Semaglutide. Front Endocrinol (Lausanne). 2019 Apr 12;10.

[37] Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. (2018) 41:258–66.

[38] Twarog C, Fattah S, Heade J, Maher S, Fattal E, Brayden DJ. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10). Pharmaceutics. 2019 Feb 13;11(2):78.

[39] Fonseca VA, Capehorn MS, Garg SK, Jodar Gimeno E, Hansen OH, Holst AG, et al. Reductions in Insulin Resistance are Mediated Primarily via Weight Loss in Subjects with Type 2 Diabetes on Semaglutide. J Clin Endocrinol Metab. 2019 Sep 1;104(9):4078–86.

[40] Christou GA, Katsiki N, Blundell J, Fruhbeck G, Kiortsis DN. Semaglutide as a promising antiobesity drug. Obesity Reviews. 2019 Jun;20(6):805–15.

[41] Smits MM, Van Raalte DH. Safety of Semaglutide. Front Endocrinol (Lausanne). 2021;12:645563.

[42] Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People with Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018 Oct 1;41(10):2127–35.

[43] Jafar N, Edriss H, Nugent K. The Effect of Short-Term Hyperglycemia on the Innate Immune System. Am J Med Sci. 2016 Feb;351(2):201–11.

[44] Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab. 1992;18(3):187–201.

[45] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020 Mar;395(10229):1033–4.

[46] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Apr;8(4):420–2.

[47] Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The Metabolic Syndrome. Endocr Rev. 2008 Dec 1;29(7):777–822.

[48] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and Management of the Metabolic Syndrome. Circulation. 2005 Oct 25;112(17):2735–52.

[49] Colditz GA. Weight Gain as a Risk Factor for Clinical Diabetes Mellitus in Women. Ann Intern Med. 1995 Apr 1;122(7):481.

[50] Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. Int J Obes. 2010;34(6):949–59.

[51] Bogardus C, Tataranni PA. Reduced Early Insulin Secretion in the Etiology of Type 2 Diabetes Mellitus in Pima Indians. Diabetes. 2002 Feb 1;51(suppl_1):S262–4.

[52] Mittendorfer B, Magkos F, Fabbrini E, Mohammed BS, Klein S. Relationship Between Body Fat Mass and Free Fatty Acid Kinetics in Men and Women. Obesity. 2009 Oct;17(10):1872–7.

[53] Karpe F, Dickmann JR, Frayn KN. Fatty Acids, Obesity, and Insulin Resistance: Time for a Reevaluation. Diabetes. 2011 Oct 1;60(10):2441–9.

[54] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology. 2004 Dec;40(6):1387–95.

[55] Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proceedings of the National Academy of Sciences. 2009 Sep 8;106(36):15430–5.

[56] Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. Journal of Clinical Investigation. 2005 May 2;115(5):1343–51.

[57] Gastaldelli A, Miyazaki Y, Pettiti M, Matsuda M, Mahankali S, Santini E, DeFronzo RA, Ferrannini E. Metabolic effects of visceral fat accumulation in type 2 diabetes. J Clin Endocrinol Metab. 2002 Nov;87(11):5098-103.

[58] ter Horst KW, Vatner DF, Zhang D, Cline GW, Ackermans MT, Nederveen AJ, et al. Hepatic Insulin Resistance is not Pathway Selective in Humans with Nonalcoholic Fatty Liver Disease. Diabetes Care. 2021 Feb 1;44(2):489–98.

[59] Smith GI, Polidori DC, Yoshino M, Kearney ML, Patterson BW, Mittendorfer B, et al. Influence of adiposity, insulin resistance, and intrahepatic triglyceride content on insulin kinetics. Journal of Clinical Investigation. 2020 May 18;130(6):3305–14.

[60] Cohen RV, Pereira TV, Aboud CM, Petry TBZ, Lopes Correa JL, Schiavon CA, et al. Effect of Gastric Bypass vs Best Medical Treatment on Early-Stage Chronic Kidney Disease in Patients With Type 2 Diabetes and Obesity. JAMA Surg. 2020 Aug 19;155(8):e200420.

[61] Gomez-Ambrosi J, Andrada P, Valenti V, Rotellar F, Silva C, Catalan V, et al. Dissociation of body mass index, excess weight loss and body fat percentage trajectories after 3 years of gastric bypass: relationship with metabolic outcomes. Int J Obes. 2017;41(9):1379–87.

[62] Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L et al. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA 2013; 310: 2416–2425.

[63] McClung JA, Naseer N, Saleem M, Rossi GP, Weiss MB, Abraham NG, et al. Circulating endothelial cells are elevated in patients with type 2 diabetes mellitus independently of HbA1c. Diabetologia. 2005 Feb 20;48(2):345–50.

[64] El-Seweidy MM, sarhan Amin R, Husseini Atteia H, El-Zeiky RR, Al-gabri NA. Dyslipidemia induced inflammatory status, platelet activation and endothelial dysfunction in rabbits: Protective role of 10-Dehydrogingerdione. Biomedicine & Pharmacotherapy. 2019 Feb;110:456–64.

[65] Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Rev Endocrinol. 2009 Mar;5(3):150–9.

[66] Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019 Aug 16;5(1):56.

[67] Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. Clinical Diabetes. 2008 Apr 1; 26(2):77–82.