Key Modifiers of Glucose Metabolism Associated Diseases (GMADs): A Mini Review

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Abstract

Glucose metabolism associated diseases (GMAD) augmentation is perilous for both nation's economy and individual life expectancy. Type 2 diabetes mellitus consists 90% among all kinds of diabetes. According to a global survey of International Diabetes Federation every 2/3 T2DM people have a risk of cardiovascular disease i.e. uncontrolled blood glucose level, high blood pressure, high cholesterol. As per WHO, diabetes will be the seventh prime cause of death globally by 2030. By 2030 the expected diabetic number is 578 million and at present it is approximately 422 million. There are a number of drugs are available such as sulphonylureas, biguanides, insulin, acarboses to treat GMAD.

This review summarizes the therapeutics available for GMAD, specially the glucagon like peptide-1 receptor agonists and their outcomes in various trials. This review also emphasize the complications associated with GMAD.

Keywords: *Glucose metabolism associated diseases (GMAD), diabetic complications, GLP-1 agonists, semaglutide, therapeutics for GMAD*

1. Introduction

Glucose metabolism associated diseases (GMADs) prevalence affects people globally. GMADs are perilous for both the nation's economy and individual life expectancy. Most common among GMAD is type 2 diabetes mellitus that is 90% among all the diabetes. Sulphonylureas, biguanides, DPP4i, SGLT2i, GLP-1RAs are prevalent therapeutics nowadays. Various factors contribute their role in causing GMAD such as complications in hemodynamic includes disturbance in blood pressure and fluid balance; genetic includes susceptibility and gene expression; metabolic complications include glycaemic and lipid control. These all activities cause cellular damage by gene modifications, protein expression and modification that later results in immune system recruitment and ultimately causes cellular dysfunction and death (Forbes; 2013). Outcome of these complications are grouped under micro vascular diseases which are caused by damage of small blood vessels and macrovascular diseases caused by damage of arteries (Avogaro et al; 2019).

Glucose metabolism is a complex process in which the body breaks down carbohydrates into glucose next to cascade signaling and plies it for energy production. Glucose metabolism is provoked in many aspects such as by peripheral insulin, adipocyte insulin, hepatic insulin, Beta-cell responsiveness (Poggiogalle; 2018). When this process is disrupted, it can lead to various diseases and conditions (Chen; 2019) (Nakrani; 2022). Some of the key diseases associated with glucose metabolism comprises diabetes mellitus, hypoglycaemia, *Hyperglycemia* metabolic syndrome, gestational diabetes, insulin resistance, prediabetes, Glycogen storage diseases, insulinoma, cushing's syndrome, certain liver diseases (i.e. NAFLD), polycystic ovary syndrome (PCOS) (Douillard *et al*; 2020) (Iqbal et al; 2016) (Otto et al; 1996) (Amiel; 2021) (Sharma; 2020) (Anagnostis; 2020) (Shearer; 2022) (Zhang; 2022) (American Diabetes Association; 2009) (International Diabetic Federation; 2017). (Figure 1).

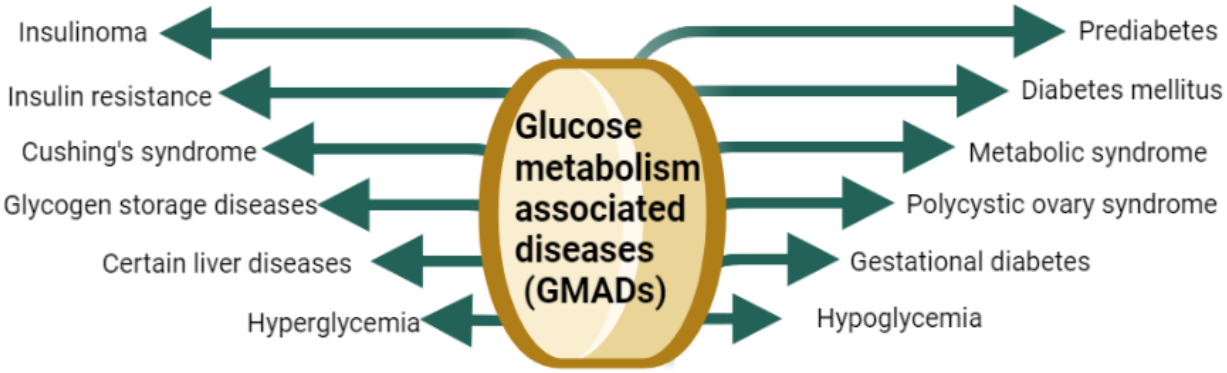

Figure 1. Diagram showing the different diseases associated with glucose metabolism

Diabetes is one of the distressed GMADs booming worldwide and affecting different organs of the body such as eyes, kidneys, brain, liver, heart, somatic nerves, autonomic nerves, blood vessels, feet. (Jones & Edwards; 2010) (Avogaro et al; 2019) (Zakin et al; 2019). If diabetes remains uncontrolled unremittingly then it may be lethal by multi organ failure. (Gerstein; 2013) (Redondo; 2020). CKD is most likelihood to occur if uncontrolled diabetes last for several years (Shepard; 2019). Resulting complication are grouped under various categories (Figure 2) and (Figure 3). Apart from the complications giving in figure 2 there exists other complication also that affects heart, brain, vessels, bone marrow (Avogaro et al; 2019). Diabetic retinopathy, diabetic nephropathy and diabetic neuropathy are the popular indication of microvascular diseases (Beckman et al; 2016) (Abid et al; 2022) (Samsu; 2021). Microvascular consequences can be reduced by the multi insulin therapy and conventional insulin therapy (Shichiri et al; 2000). There is high prevalence of microvascular diseases in US in the last thirty years that causes severity in the population and giving rise to other severe complications (Fang et al; 2021). Most commonly used therapeutics for GMADs are listed in table 1.

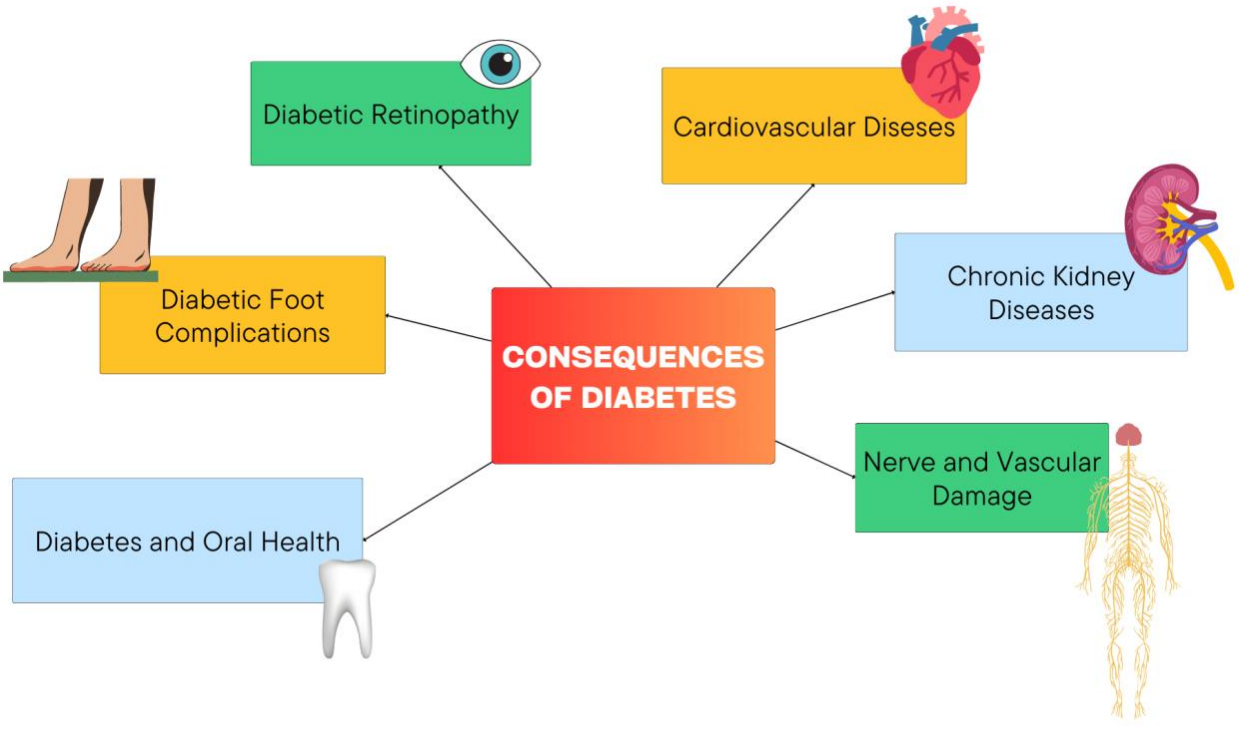

Figure 2. Consequences of diabetes. Various consequences occurs in diabetes, most common are shown in this diagram.

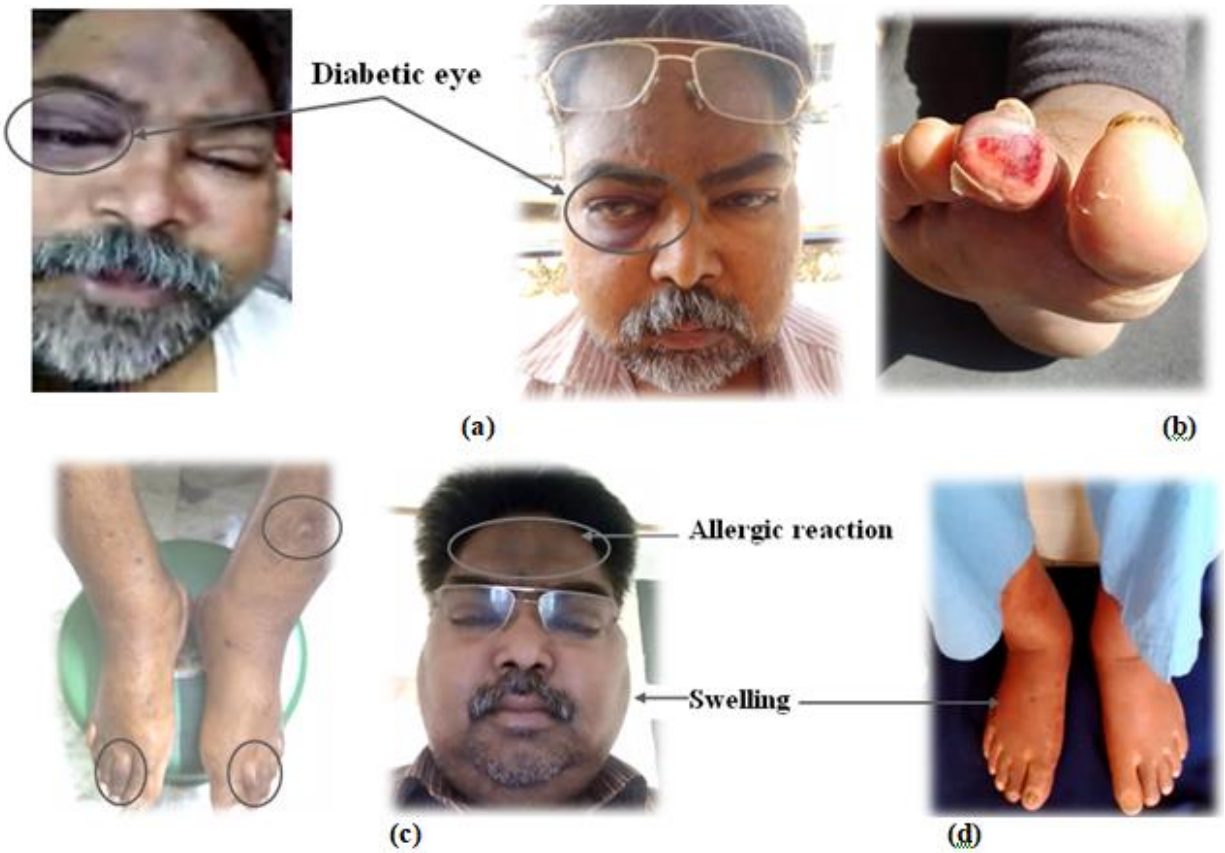

Figure 3. (a) This picture illustrating a diabetic patient's eye suffering from diabetic retinopathy. It remains asymptomatic in the early phases. Functional changes in electroretinography (ERG), retinal blood vessel calibre, retinal blood flow might be the basis of diagnosis of diabetic retinopathy. Severity in diabetic retinopathy may lead to further dangerous complication such as diabetic macular edema, retinal ischaemia. (b) Illustrating the diabetic feet (c) circled area represent the damage occurred in feet due to diabetic nephropathy. Diabetic neuropathy is characterized by nerve damage and causes pain in feet, loss of sensation, sleeping difficulty, chances of getting foot ulcers. This problem seems in older age due to time taken by nerve damage (d) Picture showing the adverse effects of CKD such as skin allergy, swelling in body due to improper kidney functioning

Table 1 List of available therapeutics for GMADs

S. No.	Drug Class	Drug Name	Drug Bank Accession Number	Brand Names	Approved status	Generation	Doses	Hypoglycemia Effect	Weight change
1.	Sulphonylureas	Gliclazide	DB01120	Diamicron	Approved	Second generation	80-320 mg	hypoglycemia	Gain
2.		Gliclazide MR		Diamicron	Approved	Second generation		Reduced risk of hypoglycemia	Gain
3.		Glimepiride	DB00222	Amaryl, Duetact, Tandemact	Approved	Second generation	1-8 mg	hypoglycemia	Gain
4.		Glipizide	DB01067	Glucotrol	Approved, Investigational	Second generation	5-20 mg	hypoglycemia	Gain
5.		Glyburide	DB01016	Diabeta, Glucovance, Glynase	Approved	Second generation	1.25-20 mg	hypoglycemia	Gain
6.	Alphaglucosidase inhibitor	Acarbose	DB00284	Precose		-		No	
7.		Miglitol	DB00491			Second generation		No	
8.	Thiazolidinedione	Pioglitazone	DB01132	Actoplus Met, Actos, Duetact, Incresync, Oseni, Tandemact			45 mg	No	Gain
9.		Rosiglitazone	DB00412	Avandamet, Avandia	Approved,		8 mg	No	Gain

					Investigational				
10.		Troglitazone	DB00197	-	Approved, Investigational, Withdrawn			No	
11.	Dipeptidyl peptidase-4 inhibitor	Algogliptin					25 mg	No	Neutral
12.		Linagliptin	DB08882	Glyxambi, Jentadueto, Tradjenta, Trajenta, Trijardy	Approved		5 mg	No	Neutral
13.		Saxagliptin	DB06335	Kombiglyze, Komboglyze, Onglyza, Qtern, Qternmet	Approved		10 mg	No	Neutral
14.		Sitagliptin	DB01261	Janumet, Januvia, Ristaben, Steglujan, Tesavel, Velmetia, Xelevia	Approved, Investigational		100 mg	No	Neutral
15.		Vildagliptin	DB04876	Galvus, Jalra, Xiliarx	Approved, Investigational		100 mg	No	Neutral
16.	Sodium glucose transporter-2 inhibitor	Canagliflozin	DB08907	Invokamet, Invokana	Approved		300 mg	No	Loss (Inermediate)
17.		Dapagliflozin	DB06292	Edistride, Farxiga, Forxiga, Qtern, Qternmet, Xigduo	Approved		10 mg	No	Loss (Inermediate)

18.		Empagliflozin	DB09038	Glyxambi, Jardiance, Synjardy, Trijardy	Approved		25 mg	No	Loss (Inermediate)
19.		Ertugliflozin	DB11827	Segluromet, Steglatro, Steglujan	Approved, Investigational		15 mg	No	Loss (Inermediate)
20.	Glucagon like peptide-1 receptor agonist	Semaglutide (Oral)	DB13928	Ozempic, Rybelsus, Wegovy	Approved, Investigational		1 mg	No	Loss
21.	Biguanide	Metformin	DB00331	Actoplus Met, Avandamet, Fortamet, Glucophage, Glucovance, Glumetza, Glycon, Invokamet, Janumet, Jentadueto, Kazano, Kombiglyze, Komboglyze, Qternmet, Riomet, Segluromet, Synjardy, Trijardy, Velmetia, Xigduo	Approved		500-2550 mg	No	Neutral (Potential for modest loss)

2. Recommended therapeutics for optimal glycemic control from initiation to intensification as per by different federations

2.1 As per American Diabetes Association (ADA) 2022, metformin monotherapy and lifestyle modification. In the first intensification dual combination of the treatment of glycemic control those agents have to be incorporated which has adequate efficacy in such as glucagon like peptide-1 receptor agonists, thiazolidinediones, sulphonylureas, insulin. Second intensification triple combination involves additional comorobidities, patient-centred treatment factors and management needs in choice of therapy based on need to to minimize weight gain or promote weight loss, minimize hypoglycemia, minimize cost. Third intensification involves incorporation of additional agents based on comorbidities, patient-centred treatment factors and management needs (Draznin et al; 2022).

2.2 As per American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD) 2022, Metformin or equivalent with combination therapy provides adequate efficacy to achieve and maintain the treatment goal. In general higher efficacy approaches have greater likelihood of achieving glycemic control. Dulaglutide (high dose), semaglutide, tirzepatide, insulin, combination oral, combination injectable i.e. GLP-1RAs or insulin have very high efficacy whilst other GLP-1RAs, metformin, SGLT2i, SU, TZD have high efficacy and DPP4i have moderate efficacy. Obstacle identification if treatment goals are unable to be reached by self management education and support (DSMES). Routine glucose monitoring. Identify social determinants of health that impact the goal achievement. (Davies et al; 2022)

2.3 As per International Diabetes Federation (IDF) 2017, IDF 2017 suggests metformin as monotherapy. If metformin is contraindicated then either DPP4i, AGI or SUs (except glibenclamide and glyburide). If baseline HbA_{1c} is 1-2% above target. (i.e 7.5-9%) then combination therapy used in which metformin with either SUs (except glibenclamide and glyburide) or DPP-4i or SGLT-2i is recommended. In Asia GLP-1RA and AGI are recommended as combination therapy with metformin. Most common choice is to add basal insulin (IDF, 2017) (Cosentino et al; 2020).

2.4 As per European Society of Cardiology (ESC)/ European Association for the Study of Diabetes (EASD)2019, The ESC or EASD also recommends metformin as monotherapy. And in dual combination DPP-4i, GLP-1RA, SGLT-2i or TZD can be used. If this double combinations function go on the blink than add higher generations sulfonylureas or basal insulin.

2.5 As per National Institute for Health and Care Excellence (NICE) 2022, metformin is the first line therapy; however, if there is some gastrointestinal disturbance then metformin XR is recommended. In case, metformin is contraindicated, sulphonylureas or SGLT-2inhibitors are the alternative options. When there is still uncontrolled HbA_{1c} below the person's individual goal then add on insulin based therapy.

3. Recommended therapeutics for GMAD patients to minimize weight gain

3.1 As per ADA, 2022, for obsessed people metformin monotherapy along with moderate physical activity at least for 150 minutes per week is recommended to achieve approximately 5% weight loss. First intensification dual combination includes addition of a GLP-1RA with weight loss efficacy or an SGLT-2i. Second intensification triple combination included addition of GLP-1RA if patient is on SGLT-2i or SGLT-2i if patient is on GLP-1RA. If GLP-1RA is contraindicated than can be replaced with weight neutral DPP-4i. Third intensification includes addition of other agents as per the patients centered treatment.

3.2 As per ADA or EASD 2022, medical nutritional therapy, physical activity, diet plan, and general lifestyle is recommended. Medication is suggested to minimize weight gain or to promote weight loss, metabolic surgery is suggested, if required. Glucose lowering drugs are suggested to be chosen with high (i.e. dulaglutide, liraglutide) to very high (i.e. semaglutide, terzepatide) dual glucose and weight efficacy. It is advisable to follow the diabetes self management education and support, analyze your blood glucose level by continuous glucose monitoring. Identify the social determinants of health that impact the goal achievement. Most widely used GLP-1RAs are listed in Table 2 and their chemical information is listed in table 3.

Table 2: Available GLP-1 agonists for the treatment of diabetes type 2

S. No.	GLP-1 Agonists	Drug Brand Name	DrugBank Accession Number	Drug Marketed by	Approval Year	Adverse effect
1.	Albiglutide	Eperzan, Tanzeum	DB09043	GlaxoSmithKline (GSK)	2014	Must not used if patient has family history of multiple endocrine neoplasia (MEN2)
2.	Dulaglutide	Trulicity	DB09045	Eli Lilly	2014 ((For DT2), 2020 (For both DT2 & prevention of cardiovascular events)	Diarrhea, Nausea, Vomiting, decreased appetite, indigestion, fatigue

3.	Exenatide	Bydureon, Byetta	DB01276	AstraZeneca	2005	Constipation, Diarrhea, Nausea, Vomiting, Headache, Dizziness
4.	Liraglutide	Saxenda, Victoza, Xultophy	DB06655	Novo Nordisk	2010	Constipation, Diarrhea, Nausea, Vomiting, Upper respiratory tract infection, Pancreatitis
5.	Lixisenatide	Adlyxin Starter Kit, Adlyxine, Lyxumia, Soliqua	DB09265	Sanofi-Aventis	2016	Nausea, Dizziness, Pancreatitis, headached, kidney problems
6.	Semaglutide	Ozempic, Rybelsus, Wegovy	DB13928	Novo Nordisk	2017 (subcutaneous injection), 2019 (oral administration), 2021 (chronic weight management)	Alergic reactions,(hives, itching, dizziness, breathing difficulty), swelling on face, kidney problems, Must not used if patient has family history of multiple endocrine neoplasia (MEN2)
7.	Taspoglutide	NA	DB14027	NA	under investigation	NA

Table 3: Chemical information of the available GLP-1 agonists listed in Table 2

S. No.	GLP-1 Agonists	Chemical formula	Average weight (Da)	Target	Enzyme	Carrier
1.	Albiglutide	$C_{3232}H_{5032}N_{864}O_{979}S_{41}$	72970.0	GLP-1R	DPP-4	Serum Albumin
2.	Dulaglutide	$C_{2646}H_{4044}N_{704}O_{836}S_{18}$	59669.81	GLP-1R		
3.	Exenatide	$C_{184}H_{282}N_{50}O_{60}S$	4186.6	GLP-1R	DPP-4,	Serum Albumin
4.	Liraglutide	$C_{172}H_{265}N_{43}O_{51}$	3751.2	GLP-1R	DPP-4, Neprilysin	Serum Albumin
5.	Lixisenatide	$C_{215}H_{347}N_{61}O_{65}S$	4858.56	GLP-1R		
6.	Semaglutide	$C_{187}H_{291}N_{45}O_{59}$	4113.641	GLP-1R	DPP-4, Neprilysin, Lipopritein Lipase, Alpha amylase	Serum Albumin
7.	Taspoglutide	$C_{152}H_{232}N_{40}O_{45}$	3339.763			

Table 4: Treatment recommendation for GMADs as per the goal of therapy

S. No.	Disease	Goal of therapy	Treatment	Remark
1.	CKD with albuminuria i.e. >= 200mg/g	Reduce CKD progression	• Primary SGLT-2i • GLP-1RA if SGLT-2i not tolerated	
2.	CKD without albuminuria i.e. eGFR<60ml/min/1.73 m^2	Reduce CKD progression	• Either GLP-1RA or SGLT-2i • If already on SGLT-2i then add GLP-1RA or vice versa	
3.	T2DM (with less increment in HbA_{1c})	Reduce HbA_{1c} and BMI	• GLP-1RA • SGLT-2i can be used but not preferred because there is not a specific cardiovascular risk	

			• If there is effect on weight using GLP-1RA than SUs second generation recommended • DPP-4i can be used but not preferred because there is no hypoglycemia risk	
4.	T2DM (with cardiovascular and/or renal morbidity)	Reduce HbA_{1c}	• GLP-1RA, SGLT-2i, DPP-4i	
5.	T2DM with cardiovascular disease (with past history of myocardial infarction)	Reduce HbA_{1c}	• Monotherapy with SGLT-2i or GLP-1RA.	Avoid Pioglitazone, it can cause oedema and heart failure
6.	CKD stage 4	Reduce effect of CKD	• GLP-1RA preferd due to cardiovascular benefits and possibly kidney benefits	Metformin and SGLT-2i are contraindicated
7.	Peripheral vascular disease with diabetes	Target HbA_{1c} 7%	• SGLT-2i, GLP-1RA	

4. Recommended therapeutics for Atherosclerotic Cardiovascular Disease (ASCVD) patients or patients with high Cardiovascular diseases (CVD) risk

4.1 As per ESC/EASD 2019, SGLT-2i or GLP-1RA monotherapy is recommended followed by the addition of metformin or other class with proven CVD benefits as needed. Low dose of thiazolidinedione may be better tolerated though less well-studied for CVD effects. DPP-4i can be added if paient is not on GLP-1RA. Basal insulin, sulphonylureas may be the alternatives.

4.2 As per ADA 2022, if there is target organ damage or multiple risk factors then either GLP-1RA or SGLT-2i can be given with proven CVD benefits. If the patients is on GLP-1RA then a SGLT-2i with proven CVD benefit can be incorporated and vice versa. Low-dose thiazolidindione could be the option though less studied for CVD effects. (Draznin et al; 2022) (Cosentino et al; 2020) (Davies et al, 2022)

4.3 As per NICE 2022, metformin is recommended in the starting and after confirming the tolerability SGLT-2i with proven CVD benefit can be added. If metformin is not tolerated than SGLT-2i is recommended alone. If there is case of established ASCVD or high CVD risk ten switching or adding different classes drug is recommended. Consider SGLT-2i if not prescribed before (NICE guidelines; 2022).

4.4 As per ADA/EASD 2022, SGLT-2i or GLP-1RA with CVD proven benefits recommended as an initiation therapy. If the patients are taking GLP-1RA then a SGLT-2i with proven CVD benefit is recommended and vice versa (Draznin et al; 2022) (Cosentino et al; 2020) (Davies et al, 2022). If goals are still not achieving then identify the obstacles using continuous glucose monitoring, consider diabetes self-management education and support and also identify the social determinants of health.

5. Recommended therapeutics from initiation to intensification for patients with heart failure

5.1 As per ESC/EASD (2019), SGLT-2i or GLP-1RA is recommended as monotherapy. For dual combination metformin is recommended. Addition of other classes of SGLT-2i or GLP-1RA with proven heart failure benefit is recommended. Consider DPP-4i if not on GLP-1RA. Sulphonylureas can be added as triple combination if required.

5.2 As per ADA 2022, SGLT-2i with proven heart failure benefit is recommended. If HbA_{1c} remains above target then add treatment as per the management needs. Recommended therapeutics for GMADs as per the goal of therapy is listed in Table 4.

6. Recommended therapeutics from initiation to intensification for patients with CKD

6.1 As per ADA 2022, CKD patients with albuminuria i.e. ≥ 200mg/g creatinine is recommended with SGLT-2i and then adding GLP-1RA and vice versa if monotherapy of either GLP-1RA or SGLT-2i is contraindicated. Evidence of reducing CKD progression using these therapies is suggested from cardiovascular outcome trials (CVOTs) (Yau et al; 2022).

6.2 As per ADA/EASD 2022, CKD patients with ACR ≥ 3.0 mg/mmol or eGFR < 60ml/min 1.73 m^2 preferably recommended with SGLT-2i with primary evidence of reducing CKD progression. If SGLT-2i is not tolerated than add GLP-1RA with proven CVD benefits. If the patient is already on GLP-1RA and contraindicated then consider adding SGLT-2i. (Davies et al; 2022).

If still not achieving goals then identify the barriers by self analysis and continuous glucose monitoring. Also identify social determinants of health that impact goal achievement.

6.3 Recommended glucose lowering drugs for various stages of CKD are listed in table 5. In CKD stage 4 (eGFR 15-29 ml/min/1.73m^2) metformin and SGLT-2i are contraindicated and dose reduction required. GLP-1RA are generally preferred.

Table 5: Treatment recommendation for CKD patients with different GFRs

Patients GFRs (ml/min/1.73 m^2**)**	**Treatment**
85 with proteinuria	Gliclazide MR, DPP4i (i.e. saxagliptin/linagliptin), SGLT-2i (i.e. empagliflozin/canagliflozin/ dapagliflozin), GLP-1RA (lixisenatide/ liraglutide/ injectable semaglutide/ dulaglutide)
85 without proteinuria	Any glucose lowering drug
45	Metformin, Gliclazide MR,
42	SGLT-2i (empagliflozin) if eGFR≥20 ml/min/1.73m^2
	SGLT-2i (empagliflozin/canagliflozin) if eGFR≥30 ml/min/1.73m^2
	SGLT-2i (canagliflozin) if eGFR in between 30-90 ml/min/1.73m^2
	GLP-1RA (lixisenatide/ albiglutide/exenatide/oral semaglutide) if eGFR≥30 ml/min/1.73m^2
	GLP-1RA (liraglutide/ dulaglutide) if eGFR≥15 ml/min/1.73m^2
	GLP-1RA (injectable semaglutide) if patient NOT on dialysis
	DPP4i (i.e. sitagliptin) if eGFR≥30 ml/min/1.73m^2
	DPP4i (i.e. alogliptin) if patient NOT on dialysis
	DPP4i (i.e. linagliptin) if eGFR≥15 ml/min/1.73m^2
<30	Gliclazide MR if eGFR<60 ml/min/1.73m^2
	GLP-1RA (injectable semaglutide) if patient NOT on dialysis
	GLP-1RA (liraglutide/ dulaglutide) if eGFR≥15 ml/min/1.73m^2
	DPP4i (i.e. alogliptin) if patient NOT on dialysis
	DPP4i (i.e. saxagliptin/ linagliptin) if eGFR≥15 ml/min/1.73m^2

7. Conclusion

After a number of surveys by different federations they recommended various treatments for GMADs . From all those recommendations we concluded that there are a number of classes for glucose lowering drugs such as GLP-1RA, SUs, SGLT-2i. More suitable medicines for lowering blood glucose with different conditions are as follows:

- DPP4i, insulin, GLP-1RA if a person has a history of heart failure, high risk ASCVD, eGFR < 15 ml/min/1.73 m2 or on dialysis
- SUs, TZD if the patient willing the treatment at low cost.
- GLP-1RA in case of obesity
- DPP-4i, TZD, AGI, Oral GLP-1RA if patient wants to avoid injection
- GLP-1RA, DPP-4i, TZD, AGI to avoid hypoglycemia.

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References

[1] *Abid, F., Rubab, Z., Fatima, S., Qureshi, A., Azhar, A., & Jafri, A. (2022). In-silico analysis of interacting pathways through KIM-1 protein interaction in diabetic nephropathy. BMC nephrology, 23(1), 254. https://doi.org/10.1186/s12882-022-02876-7*

[2] *American Diabetes Association; Standards of Medical Care in Diabetes (2009). Diabetes Care ; 32 (Supplement_1): S13–S61. https://doi.org/10.2337/dc09-S013*

[3] *Amiel S. A. (2021). The consequences of hypoglycaemia. Diabetologia, 64(5), 963–970. https://doi.org/10.1007/s00125-020-05366-3*

[4] *Anagnostis, P., & Goulis, D. G. (2020). Cushing's Syndrome and Cardiovascular Risk. Current vascular pharmacology, 18(1), 25–26. https://doi.org/10.2174/1570161117999190318142847*

[5] *Avogaro, A., & Fadini, G. P. (2019). Microvascular complications in diabetes: A growing concern for cardiologists. International journal of cardiology, 291, 29–35. https://doi.org/10.1016/j.ijcard.2019.02.030*

[6] *Beckman, J. A., & Creager, M. A. (2016). Vascular Complications of Diabetes. Circulation research, 118(11), 1771–1785. https://doi.org/10.1161/CIRCRESAHA.115.306884*

[7] *Carracher, A. M., Marathe, P. H., & Close, K. L. (2018). International Diabetes Federation 2017. Journal of diabetes, 10(5), 353–356. https://doi.org/10.1111/1753-0407.12644*

[8] *Charles, C., & Ferris, A. H. (2020). Chronic Kidney Disease. Primary care, 47(4), 585–595. https://doi.org/10.1016/j.pop.2020.08.001*

[9] *Chen, Y., Zhao, X., & Wu, H. (2019). Metabolic Stress and Cardiovascular Disease in Diabetes Mellitus: The Role of Protein O-GlcNAc Modification. Arteriosclerosis, thrombosis, and vascular biology, 39(10), 1911–1924. https://doi.org/10.1161/ATVBAHA.119.312192*

[10] *Cosentino, F., Grant, P. J., Aboyans, V., Bailey, C. J., Ceriello, A., Delgado, V., Federici, M., Filippatos, G., Grobbee, D. E., Hansen, T. B., Huikuri, H. V., Johansson, I., Jüni, P., Lettino, M., Marx, N., Mellbin, L. G., Östgren, C. J., Rocca, B., Roffi, M., Sattar, N., ... ESC Scientific Document Group (2020). 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European heart journal, 41(2), 255–323. https://doi.org/10.1093/eurheartj/ehz486*

[11] *Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., Rosas, S. E., Del Prato, S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A., & Buse, J. B. (2022). Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care, 45(11), 2753–2786. https://doi.org/10.2337/dci22-0034*

[12] *Dodds S. (2017). The How-To for Type 2: An Overview of Diagnosis and Management of Type 2 Diabetes Mellitus. The Nursing clinics of North America, 52(4), 513–522. https://doi.org/10.1016/j.cnur.2017.07.002*

[13] *Douillard, C., Jannin, A., & Vantyghem, M. C. (2020). Rare causes of hypoglycemia in adults. Annales d'endocrinologie, 81(2-3), 110–117. https://doi.org/10.1016/j.ando.2020.04.003*

[14] *Draznin, B., Aroda, V. R., Bakris G., et al (American Diabetes Association Professional Practice Committee) (2022). 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022. Diabetes Care ; 45 (Supplement_1): S125–S143. https://doi.org/10.2337/dc22-S009*

[15] *Fang, M., & Selvin, E. (2021). Thirty-Year Trends in Complications in U.S. Adults With Newly Diagnosed Type 2 Diabetes. Diabetes care, 44(3), 699–706. https://doi.org/10.2337/dc20-2304*

[16] *Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of diabetic complications. Physiological reviews, 93(1), 137–188. https://doi.org/10.1152/physrev.00045.2011*

[17] *Gerstein, H. C., & Werstuck, G. H. (2013). Dysglycaemia, vasculopenia, and the chronic consequences of diabetes. The lancet. Diabetes & endocrinology, 1(1), 71–78. https://doi.org/10.1016/S2213-8587(13)70025-1*

[18] *International Diabetic Federation (2017). Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care.*

[19] *Iqbal, A., & Heller, S. (2016). Managing hypoglycaemia. Best practice & research. Clinical endocrinology & metabolism, 30(3), 413–430. https://doi.org/10.1016/j.beem.2016.06.004*

[20] *Jones, S., & Edwards, R. T. (2010). Diabetic retinopathy screening: a systematic review of the economic evidence. Diabetic medicine : a journal of the British Diabetic Association, 27(3), 249–256. https://doi.org/10.1111/j.1464-5491.2009.02870.x*

[21] *Lassalle, M., Monnet, E., Ayav, C., Hogan, J., Moranne, O., Couchoud, C., & REIN registry (2019). 2017 Annual Report Digest of the Renal Epidemiology Information Network (REIN) registry. Transplant international : official journal of the European Society for Organ Transplantation, 32(9), 892–902. https://doi.org/10.1111/tri.13466*

[22] *Nakrani M. N., Wineland R. H., & Anjum F. (2022). Physiology, Glucose Metabolism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; https://www.ncbi.nlm.nih.gov/books/NBK560599/*

[23] *National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guidelines (2015, 2022 updated). https://www.nice.org.uk/guidance/ng28*

[24] *Neyra, J. A., & Chawla, L. S. (2021). Acute Kidney Disease to Chronic Kidney Disease. Critical care clinics, 37(2), 453–474. https://doi.org/10.1016/j.ccc.2020.11.013*

[25] *Otto-Buczkowska, E., & Jarosz-Chobot, P. (1996). Hipoglikemia--problem w insulinoterapii? [Hypoglycemia--a problem in insulin therapy?]. Przeglad lekarski, 53(6), 497–500.*

[26] *Poggiogalle, E., Jamshed, H., & Peterson, C. M. (2018). Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism: clinical and experimental, 84, 11–27. https://doi.org/10.1016/j.metabol.2017.11.017*

[27] *Redondo, M. J., Hagopian, W. A., Oram, R., Steck, A. K., Vehik, K., Weedon, M., Balasubramanyam, A., & Dabelea, D. (2020). The clinical consequences of heterogeneity within and between different diabetes types. Diabetologia, 63(10), 2040–2048. https://doi.org/10.1007/s00125-020-05211-7*

[28] *Samsu N. (2021). Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. BioMed research international, 2021, 1497449. https://doi.org/10.1155/2021/1497449*

[29] *Sharma, A., & Vella, A. (2020). Glucose metabolism in Cushing's syndrome. Current opinion in endocrinology, diabetes, and obesity, 27(3), 140–145. https://doi.org/10.1097/MED.0000000000000537*

[30] *Shichiri, M., Kishikawa, H., Ohkubo, Y., & Wake, N. (2000). Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes care, 23 Suppl 2, B21–B29.*

[31] *Shearer, A. M., Wang, Y., Fletcher, E. K., Rana, R., Michael, E. S., Nguyen, N., Abdelmalek, M. F., Covic, L., & Kuliopulos, A. (2022). PAR2 promotes impaired glucose uptake and insulin resistance in NAFLD through GLUT2 and Akt interference. Hepatology (Baltimore, Md.), 76(6), 1778–1793. https://doi.org/10.1002/hep.32589*

[32] *Shepard B. D. (2019). Sex differences in diabetes and kidney disease: mechanisms and consequences. American journal of physiology. Renal physiology, 317(2), F456–F462. https://doi.org/10.1152/ajprenal.00249.2019*

[33] *Varughese, S., & Abraham, G. (2018). Chronic Kidney Disease in India: A Clarion Call for Change. Clinical journal of the American Society of Nephrology : CJASN, 13(5), 802–804. https://doi.org/10.2215/CJN.09180817*

[34] *Wasserman D. H. (2009). Four grams of glucose. American journal of physiology. Endocrinology and metabolism, 296(1), E11–E21. https://doi.org/10.1152/ajpendo.90563.2008*

[35] *Yau, K., Dharia, A., Alrowiyti, I., & Cherney, D. Z. I. (2022). Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. Kidney international reports, 7(7), 1463–1476. https://doi.org/10.1016/j.ekir.2022.04.094*

[36] *Zakin, E., Abrams, R., & Simpson, D. M. (2019). Diabetic Neuropathy. Seminars in neurology, 39(5), 560–569. https://doi.org/10.1055/s-0039-1688978*

[37] Zhang, Q., Ren, J., Wang, F., Pan, M., Cui, L., Li, M., & Qu, F. (2022). Mitochondrial and glucose metabolic dysfunctions in granulosa cells induce impaired oocytes of polycystic ovary syndrome through Sirtuin 3. Free radical biology & medicine, 187, 1–16. https://doi.org/10.1016/j.freeradbiomed.2022.05.010

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Abbreviations:

ACR	Urine albumin to creatinine ratio
ADA	American Diabetes Association
AGI	Alpha-glucosidase inhibitor
ASCVD	Atherosclerotic Cardiovascular Disease
CKD	Chronic kidney disease
CVDs	Cardiovascular diseases
DN	Diabetic Nephropathy
DPP-4i	Dipeptidyl peptidase-4 inhibitor
DSMES	Self Management Education And Support
EASD	European Association for the Study of Diabetes
eGFR	Estimated Glomerular Filteration Rate
ERG	Electroretinography
ESC	European Society of Cardiology
GFR	Glomerular Filtration Rate
GLP-1	Glucagon like peptide-1
GLP-1RA	Glucagon like peptide-1 receptor agonist
GMAD	Glucose metabolism associated diseases
HbA_{1c}	Glycated Hemoglobin
IDF	International Diabetes Federation
MR	Modified Release
NAFLD	Non alcoholic fatty liver disease
NICE	National Institute for Health and Care Excellence
PCOS	Polycystic ovary syndrome
SGLT-2i	Sodium glucose transporter-2 inhibitor
SUs	Sulphonylureas
T2DM	Type 2 diabetes mellitus
TZD	Thiazolindine