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Effect of the Use of DPP4 Inhibitors Alone or Combined with SGLT2 Inhibitors on HbA1c, Apolipoproteins and Renal Function of Children, Adolescents and Young People with DM1: A Cohort Study

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Abstract

Background/Objectives: Type 1 diabetes mellitus (T1DM) is a chronic autoimmune condition often managed exclusively with insulin. However, the search for adjuvant therapies has gained attention, including dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), despite limited evidence in pediatric populations. To evaluate the impact of DPP4i, alone or combined with SGLT2i, on glycemic control (HbA1c), lipid profile (ApoB and ApoA-I), and renal function (eGFR and albuminuria) in children, adolescents, and young adults with T1DM, this study was conducted. **Methods:** This cohort study analyzed data from 76 patients with T1DM aged under 25, followed for 4 to 20 months. Patients were grouped based on exposure to DPP4i alone, DPP4i + SGLT2i, or no additional therapy. Glycemic, lipid, and renal parameters were assessed at baseline and follow-up. **Results:** A significant reduction in HbA1c was observed in the overall sample ($p < 0.001$), regardless of treatment group, suggesting a positive effect of interdisciplinary care. There were no statistically significant differences in HbA1c variation among the groups. ApoB decreased significantly over time ($p < 0.001$), and ApoA-I levels were initially higher in the DPP4i + SGLT2i group. A significant reduction in albuminuria was identified in the DPP4i-only group compared to controls ($p = 0.029$), indicating a potential renoprotective effect. No significant changes in eGFR were observed. The use of DPP4i, with or without SGLT2i, was not associated with significant improvements in glycemic or lipid outcomes compared to standard therapy. However, DPP4i monotherapy was associated with a reduction in albuminuria, suggesting a possible benefit for renal protection. **Conclusions:** These findings highlight the need for larger, randomized studies to confirm the therapeutic role of these agents in young individuals with T1DM.

Keywords: type 1 diabetes mellitus; DPP4 inhibitors; SGLT2 inhibitors; glycemic control; apolipoproteins; renal function; pediatric diabetes; albuminuria

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1. Introduction

Diabetes mellitus is a pathology characterized by the body's homeostatic imbalance, resulting from changes in the ability to store glucose intracellularly, which have repercussions in several organ systems [1]. This condition is subdivided into types 1 and 2, with the first, the focus of this article, being characterized as an autoimmune disease caused by the destruction of pancreatic β cells, a process mediated by T cells. As it is a multifactorial disorder, it is vital to seek therapeutic solutions to prevent possible clinical manifestations caused by type 1 diabetes mellitus (DM1) [2].

The search for adjuvant therapies in the management of DM1 has intensified, especially given the limitations of exclusive insulin treatment. Among the emerging approaches, dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter type 2 inhibitors (SGLT2i) have been investigated for their potential to modulate glycemia and offer additional metabolic benefits. Although widely used in type 2 diabetes (T2D), their use in T1D is still considered off-label, requiring caution and rigorous investigation. Studies demonstrate that DPP4i, by preserving incretins such as GLP-1, promote insulin secretion in a glucose-dependent manner, with a low risk of hypoglycemia [3]. SGLT2i acts by promoting glycosuria, which can reduce blood glucose and glycemic variability [4].

In this sense, the use of DPP4 in DM1 is because this substrate inhibits the degradation of the hormones GLP-1 and GIP, which are incretins that stimulate insulin release. This is expected to act by modulating the glycemic levels of patients undergoing this therapy [5]. In addition to glycemic control, there is growing interest in the effects of these drugs on cardiovascular and renal parameters. SGLT2i, on the other hand, have demonstrated benefits in reducing blood pressure and renal protection in patients with type 2 diabetes mellitus (DM2), effects that can be partially extrapolated to DM1 [4]. In contrast, DPP4i have been associated with renal anti-inflammatory and antifibrotic effects, suggesting a possible role in preventing the progression of diabetic nephropathy [6]. The combination of these two classes may theoretically offer therapeutic synergism, although data in pediatric and young populations with DM1 are still scarce.

The evaluation of biomarkers such as apolipoproteins ApoB and ApoA-I has gained prominence in the stratification of cardiovascular risk in patients with diabetes. ApoB is associated with atherogenic particles, while ApoA-I is related to cardiovascular protection through reverse cholesterol transport [7]. Studies suggest that pharmacological interventions that modulate these markers can directly impact the risk of cardiovascular events, and it is relevant to investigate whether DPP4i and SGLT2i influence these parameters in young populations with DM1 [8].

In the context of renal function, albuminuria and estimated glomerular filtration rate (eGFR) are key markers for early detection of kidney injury. The literature indicates that SGLT2i promote the reduction in albuminuria and stabilization of eGFR in patients with T2DM, including in the early stages of chronic kidney disease [9]. DPP4i has demonstrated renal protective effects, possibly through anti-inflammatory mechanisms and preservation of endothelial integrity [10]. Investigation of these effects in children and adolescents with DM1 is essential, considering the increased risk of renal complications in this population. The off-label use of DPP4 inhibitors, alone or in combination with SGLT2, in patients with DM1 has been reported in the scientific literature due to the potential metabolic and renoprotective benefit of these classes, although data in pediatric populations are scarce [6,8]. Thus, our objective was to analyze the clinical outcomes associated with these practices in real-world conditions, contributing to the generation of evidence on their safety and efficacy in children, adolescents, and young adults with DM1.

Finally, it is essential to note that most available studies have been conducted in adults with T2DM, with limited data on pediatric populations with T1DM. Extrapolation

of the findings should be done with caution, taking into account the pathophysiological and pharmacokinetic particularities of this age group. The present cohort aims to contribute to the knowledge about the effects of using DPP4i alone or in combination with SGLT2i on glycemic, lipid, and renal parameters in children, adolescents, and young adults with T1DM.

2. Materials and Methods

A short and variable follow-up cohort study (4 to 20 months) was conducted without comparison groups. The initial inclusion criterion was to have performed at least one evaluation in 2022 (Initial) and one in 2023 (final), totaling 96 patients. Seventeen patients who presented HbA1c values of 10.4% at the initial moment and three patients who presented HbA1c values of 10.4% at the final moment were excluded. The final sample consisted of 76 patients. The data were obtained from the CENID database for the period 2022 to 2023. The storage and availability of CENID data were approved by the UNIMAR Ethics and Research Committee (opinion No. 7624095/2025).

For the study, the use of DPP-4 inhibitors alone or in combination with SGLT2 inhibitors (cases) during the follow-up period was considered an exposure factor. This study was observational, using data from clinical records. The researchers did not prescribe the medications; group inclusion was determined by the use recorded during follow-up, reflecting independent clinical decisions by the attending physicians. Patients who did not use the medication (controls) during the follow-up period were considered as comparators. It was not possible to obtain information on the medication's dose from the database. When accessing the patient assessment form, it was only possible to determine whether the medication was used during the follow-up period. Follow-up time was defined as the time in months between the initial and final assessments. Follow-up time was not standardized, and the time interval between the two measurements varied among patients.

To characterize the sample at baseline, data were collected on age, sex, age at diagnosis, time since diagnosis, nutritional status, and method of insulin administration. Time since diagnosis was categorized as <1 year, 1 to 5 years, and >5 years. Age was categorized into four groups: <10 years, 10–14 years, 15–19 years, and 20–24 years. Regarding the method of insulin administration, patients were categorized into two groups: Continuous Insulin Infusion System (CIIS) and Multiple Dose Insulin (MDI). Anthropometric measurements of body mass and height were used to calculate BMI. For patients up to 19 years of age, BMI was estimated by z-score and categorized as underweight, eutrophic, overweight, and obese according to the recommendations of the World Health Organization [11]. For patients over 18 years of age, BMI was calculated using the Quetelet equation and categorized according to ABESO recommendations as underweight, eutrophic, overweight, and obese [12].

Glycemic control was assessed by measuring glycated hemoglobin (HbA1c%) using the high-performance liquid chromatography (HPLC) method [13]. The dosage of ApoB and ApoA-I was performed using the nephelometry method. Renal function was assessed by estimated glomerular filtration rate (eGFR) using the CKiD equation ($eGFR = k \times Ht/SCr$, where Ht = height in cm, SCr = serum creatinine in mg/dL, with fixed k = 0.413) expressed in mL/min/1.73 m^2 and microalbuminuria (mg/g) [14]. The CKiD equation is a reliable tool for estimating GFR in children, adolescents, and young adults (up to 25 years of age) with T1D [15]. For the analysis of Albuminuria, urine samples were obtained at the first morning urination. Participants were instructed to avoid intense physical exercise and alcohol consumption 24 h before collection. The albumin/creatinine ratio (ACR), expressed in mg/g [16].

Qualitative variables are described by absolute and relative frequency distribution (%). The association between qualitative variables was analyzed using Fisher's exact test. Quan-

titative variables were described by mean and standard deviation (SD). Normality of distribution was verified using the Shapiro–Wilk test, and homogeneity of variances was assessed using the Levene test. Student's *t*-test was used to compare two paired means. The one-way ANOVA test was used to compare three independent means, followed by Tukey's post hoc test when necessary. The significance level adopted was 5% and the data were analyzed using the Jamovi (version 2.6) software.

3. Results

No significant differences were observed between the groups in terms of age, age at diagnosis, or follow-up time in the study. However, a shorter time to diagnosis was observed in the DPP4 isolated group compared to the group without use of the medication (Table 1).

Table 1. Comparison of mean and standard deviation of age, age at diagnosis, and time of diagnosis at baseline and follow-up time between groups.

Variables	Groups	N	Average	Standard Deviation	*p*-Value
Age (years)	DPP4 + SGLT2	6	17.2	4.4	0.165
	DPP4	5	12.0	3.3	
	No adjuvant medicine	65	14.3	5.2	
Age at diagnosis (years)	DPP4 + SGLT2	6	10.5	5.7	0.54
	DPP4	5	9.8	3.0	
	No adjuvant medicine	64	8.5	4.0	
Time since diagnosis (years)	DPP4 + SGLT2	6	6.67	4.0	0.012 *
	DPP4	5	2.20 [a]	1.8	
	No adjuvant medicine	65	5.94 [b]	3.9	
Follow-up time (months)	DPP4 + SGLT2	6	13.0	4.3	0.26
	DPP4	5	15.2	5.5	
	No adjuvant medicine	65	12.0	4.3	

Note: *p*-value calculated by one-way ANOVA test. * indicates significant difference between groups for *p*-value ≤ 0.05. Different superscript letters indicate significant difference between groups within the time point by Tukey's Post Hoc test for *p*-value 0.050.

No significant difference was observed in the distribution of sex proportion, age range, time of diagnosis, nutritional status, and insulin administration methods between the groups. Regardless of the group, the sex distribution in the sample is similar; the largest proportion of patients are between 10 and 19 years old, have between 1 and 5 years of diagnosis time, have a eutrophic nutritional status, and use MDI as an insulin administration method (Table 2).

Table 2. Analysis of the distribution of absolute (N) and relative (%) proportion of sex, age group, time of diagnosis, nutritional status, and method of insulin administration between groups at baseline.

Variables	Categories	Baseline Group						Total		*p*-Value
		DPP4 + SGLT2 (n = 6)		DPP4 (n = 5)		Without Medication (n = 56)				
		N	%	N	%	N	%	N	%	
Sex	Feminine	5	83.30%	1	20.00%	36	55.40%	42	55.30%	0.153
	Masculine	1	16.70%	4	80.00%	29	44.60%	34	44.70%	
Age range (age)	<10 years	0	0.00%	2	40.00%	12	18.50%	14	18.40%	0.695
	10 to 14 years old	2	33.30%	2	40.00%	21	32.30%	25	32.90%	
	15 to 19 years old	2	33.30%	1	20.00%	20	30.80%	23	30.30%	
	20 to 24 years old	2	33.30%	0	0.00%	12	18.50%	14	18.40%	

Table 2. *Cont.*

Variables	Categories	Baseline Group						Total		*p*-Value
		DPP4 + SGLT2 (n = 6)		DPP4 (n = 5)		Without Medication (n = 56)				
		N	%	N	%	N	%	N	%	
Diagnostic time	<1 year	0	0.00%	1	20.00%	3	4.60%	4	5.30%	0.133
	1 to 5 years	2	33.30%	4	80.00%	33	50.80%	39	51.30%	
	>5 years	4	66.70%	0	0.00%	29	44.60%	33	43.40%	
Initial Nutritional Status	Eutrophic	2	33.30%	5	100.00%	37	56.90%	44	57.90%	0.179
	Overweight	1	16.70%	0	0.00%	15	23.10%	16	21.10%	
	Obese	3	50.00%	0	0.00%	13	20.00%	16	21.10%	
Initial insulin administration method	MDI	6	100.00%	5	100.00%	43	66.20%	54	71.10%	0.074
	SICI	0	0.00%	0	0.00%	22	33.80%	22	28.90%	

Note: *p*-value calculated by Fisher's Exact test indicates that there is no significant association for the proportion distribution. Multiple Dose Insulin (MDI). Continuous Insulin Infusion System (CIIS).

In Table 3, no significant difference was observed between the groups at the initial and final moments, including the variation (delta) of HbA1c%. However, regardless of the group, a significant reduction in HbA1c% was observed during the follow-up period (Mean $\pm$ DP = -0.532 ± 0.872; *p*-value ≤ 0.001) in the sample. The significant reduction in HbA1c in the sample suggests that the interdisciplinary monitoring to which patients are subjected has a positive effect on improving disease control.

Table 3. Comparison of the mean and standard deviation of HbA1c for the initial, final, and delta (final–initial) moments of the sample in relation to the medication use groups.

	Groups	N	Average	Standard Deviation	*p*-Value
Initial HbA1c (%)	DPP4 + SGLT2	6	7.750	1.045	0.218
	DPP4	5	7.472	1.000	
	No adjuvant medicine	65	8.190	1.017	
Final HbA1c (%)	DPP4 + SGLT2	6	7.250	0.878	0.201
	DPP4	5	6.978	0.730	
	No adjuvant medicine	65	7.652	0.938	
HbA1c delta (%)	DPP4 + SGLT2	6	−0.500	0.713	0.990
	DPP4	5	−0.494	0.492	
	No adjuvant medicine	65	−0.538	0.915	

Note: *p*-value calculated by the one-way Anova test > 0.050 does not indicate a significant difference between the groups.

In Table 4, no significant difference was observed in the variation in ApoB and ApoA-I between the comparison groups. However, for ApoA-I, a significant difference was observed between the DPP4 + SGLT2 and no medication groups, with higher values in the DPP4 + SGLT2 group at the initial time point. In the comparison between the initial and final moments (delta) of the follow-up period, regardless of the group, no significant variation was observed in ApoA-I (Mean $\pm$ SD = -0.226 ± 15.10; *p*-value = 0.217), however a significant reduction in ApoB was observed (Mean $\pm$ DP = -3.302 ± 9.16; *p*-value ≤ 0.001).

In Table 5, no significant variation in the glomerular filtration rate was observed between the groups. For Albuminuria, no difference was observed between the groups for the initial and final moments; however, for the delta variation, a significant difference was observed between the DPP4 and no medication groups, with a greater reduction in Albuminuria in the group using DPP4. In the comparison between the initial and final moments, regardless of the group, no significant variation was observed in Albuminuria (Mean $\pm$ SD = -1.07 ± 6.77; *p*-value = 0.173) and glomerular filtration rate (Mean $\pm$ SD = -3.01 ± 19.70; *p*-value = 0.188).

Table 4. Comparison of the mean and standard deviation of ApoB and ApoA-I for the initial, final, and delta (final–initial) moments of the sample concerning the medication use groups.

	Groups	N	Average	Standard Deviation	*p*-Value
Initial ApoB (mg/dL)	DPP4 + SGLT2	6	63.711	9.43	
	DPP4	5	75.702	9.32	0.180
	No adjuvant medicine	65	72.281	12.02	
Final ApoB (mg/dL)	DPP4 + SGLT2	6	65.807	5.60	
	DPP4	5	71.174	6.62	0.665
	No adjuvant medicine	65	68.575	10.27	
ApoB delta (mg/dL)	DPP4 + SGLT2	6	2.096	3.98	
	DPP4	5	−4.529	6.94	0.321
	No adjuvant medicine	65	−3.706	9.54	
Initial ApoA-I (mg/dL)	DPP4 + SGLT2	6	152.268 **	42.02	
	DPP4	5	132.136	4.46	0.033 *
	No adjuvant medicine	65	130.969	16.13	
Final ApoA-I (mg/dL)	DPP4 + SGLT2	6	148.743	29.35	
	DPP4	5	131.430	8.84	0.102
	No adjuvant medicine	65	131.085	18.56	
ApoA-I delta (mg/dL)	DPP4 + SGLT2	6	−3.525	14.73	
	DPP4	5	−0.706	10.92	0.854
	No adjuvant medicine	65	0.116	15.55	

Note: *p*-value calculated by one-way ANOVA test. * indicates significant difference between groups. ** indicates significant difference from the group without medication by Tukey's Post Hoc test for *p*-value $\leq$ 0.050.

Table 5. Comparison of the mean and standard deviation of Albuminuria and glomerular filtration rate (eGFR) for the initial, final, and delta (final–initial) moments of the sample to the medication use groups.

	Initial DPP4	N	Average	Standard Deviation	*p*-Value
Initial Urinary Albumin (g/dL)	DPP4 + SGLT2	6	9.443	10.068	
	DPP4	5	13.425	17.804	0.114
	No adjuvant medicine	65	7.447	4.242	
Final Urinary Albumin (g/dL)	DPP4 + SGLT2	6	5.914	3675	
	DPP4	5	5.357	0.930	0.393
	No adjuvant medicine	65	7.144	3446	
Delta Urinary Albumin (g/dL)	DPP4 + SGLT2	6	−3.529	8.951	
	DPP4	5	−8.068 **	17.328	0.029 *
	No adjuvant medicine	65	−0.303	4.873	
Initial eGFR (mL/min/1.73 m^2)	DPP4 + SGLT2	6	86.079	7.348	
	DPP4	5	102.609	14.098	0.189
	No adjuvant medicine	65	100.663	19.759	
Final eGFR (mL/min/1.73 m^2)	DPP4 + SGLT2	6	89.372	11.047	
	DPP4	5	100.462	11.364	0.491
	No adjuvant medicine	65	97.009	17.295	
eGFR delta (mL/min/1.73 m^2)	DPP4 + SGLT2	6	3.292	15.691	
	DPP4	5	−2.147	13.899	0.713
	No adjuvant medicine	65	−3.654	20.481	

Note: *p*-value calculated by one-way ANOVA test. * indicates significant difference between groups. ** indicates significant difference in relation to the group without medication by Tukey's Post Hoc test for *p*-value $\leq$ 0.050.

Regarding insulin therapy, no significant differences were observed in insulin dose (U/kg) between the groups or between the initial and final periods, as shown in Table 5. This result suggests that the use of DPP4i, alone or combined with SGLT2i, did not reduce the total insulin requirement during follow-up. On the other hand, as shown in Table 6,

there was a significant reduction in the sensitivity factor over time, with a difference between the groups according to the ANOVA test ($p < 0.001$), which may reflect individual variations or the influence of follow-up time, rather than a direct effect of the medications. Future studies should explore this relationship in more detail, including dose adjustments and clinical impact.

Table 6. Comparison of mean, standard deviation (SD), mean difference, and 95% confidence interval (95% CI) of Insulin Dose and Sensitivity Factor between groups regarding the initial and final follow-up period.

Variables	Group	Initial (2022)		Final (2023)		Difference (95% CI)			*p*-Value (ANOVA)
		Mean	SD	Mean	SD	Mean	LI	LS	
Insulin/kg (U/kg)	DPP4 + SGLT2	0.80	0.28	0.86	0.26	0.05	−0.03	0.13	0.882
	DPP4	0.51	0.34	0.57	0.36	0.06	−0.02	0.14	
	No adjuvant medicine	0.90	0.27	0.93	0.29	0.02	−0.04	0.07	
Sensitivity Factor	DPP4 + SGLT2	64.6	104.0	44.2	48.1	−20.37	−60.61	19.87	<0.001 **
	DPP4	174.4	146.7	130.5	105.2	−43.96	−97.82	9.90	
	No adjuvant medicine	49.5	37.3	45.3	33.3	−4.20 *	−8.29	−0.11	

Note: ** indicates a statistically significant difference between groups based on ANOVA, adjusted for follow-up time ($p \leq 0.050$). * indicates a statistically significant difference between baseline and final periods based on the 95% confidence interval (95% CI). LI: lower limit; LS: upper limit.

4. Discussion

DPP4 inhibitors prevent the inactivation of the hormone GLP-1 by blocking the action of the DPP4 enzyme. As a consequence, there is an increase in endogenous levels of GLP-1, which causes these drugs to indirectly stimulate glucose-dependent insulin secretion and suppress glucagon secretion by pancreatic alpha cells [17]. DPP4i also decreases gastric filling, which helps prevent glycemic spikes, and has peripheral effects, such as increased glucose uptake by muscle cells [18].

Although there was no significant difference between the groups regarding HbA1c, the sample showed a significant reduction in HbA1c, reinforcing the positive impact of interdisciplinary monitoring [19,20]. Although the use of DPP4 alone or in combination with SGLT2 did not demonstrate statistical superiority, the small sample size, especially in the intervention groups, may have limited the ability to detect fundamental differences. Other studies in populations with T2DM have shown a reduction in HbA1c with the use of DPP4 inhibitors [21,22]. However, in the population with T1DM, this effect remains controversial or is less consistent.

Although some clinical studies have reported reductions in prandial insulin dose and inhibition of glucagon secretion, results regarding HbA1c remain controversial, as evidenced by meta-analyses that did not demonstrate significant advantage [23–28].

The significant reduction in ApoB in the general sample suggests a potential risk reduction in atherosclerosis over the follow-up period; the higher initial difference in ApoA-I in the group using DPP4 inhibitors associated with SGLT2 may reflect a selection of patients with a different cardiovascular profile or better prior care, since ApoA-I is associated with cardioprotective effects; and, although there was no significant difference in the variation in apolipoproteins between the groups, it is essential to emphasize the possible positive metabolic impact of clinical follow-up. However, the isolated role of the drugs needs to be investigated with a greater sample size. These results can be related to the effect of reducing fat accumulation in the myocardium and the increased expression of transcription factors, such as NRF1 and PGC1 [29].

It is noteworthy to observe the significant reduction in albuminuria in the DPP4-only group compared to the group without medication, suggesting a potential renoprotective

effect of DPP4 inhibitors. However, the lack of difference in GFR variation reinforces the idea that any renal impact, if present, may be more closely related to microalbuminuria than to global glomerular function in this short follow-up period. It is noteworthy that previous studies suggest that DPP4i can modulate inflammation and renal fibrosis, which may explain the reduction in albuminuria observed [30,31]. These results can be related to the ability of GLP-1, present in high concentrations due to DPP4i, to reduce the production of pro-inflammatory cytokines, which may lead to a reduction in chronic inflammation [18].

The reduction in albuminuria observed in the group treated with DPP-4 inhibitors alone is noteworthy, as this effect is traditionally associated with SGLT2 inhibitors. Although the underlying mechanisms are not fully elucidated, previous studies suggest that DPP-4 inhibitors may confer renal protection through pathways independent of glycemic control. These include anti-inflammatory and antifibrotic effects mediated by increased endogenous GLP-1 levels, improved endothelial function, and modulation of renal cytokine activity [32]. Such mechanisms could explain the observed decrease in albuminuria in our cohort. However, given the small sample size and observational design, these findings should be interpreted with caution and warrant confirmation in larger, randomized studies.

Previous studies suggest that DPP-4 inhibitors may reduce albuminuria independently of glycemic control, although the underlying mechanisms remain poorly understood, including possible anti-inflammatory and antifibrotic effects [32,33].

Meta-analyses specific to T1DM indicate that the use of DPP-4 inhibitors was not associated with severe adverse events such as ketoacidosis or pancreatitis, reinforcing a favorable safety profile [27,28].

It is essential to consider the limitations presented by this study when interpreting the results. This study presents several limitations that should be considered when interpreting the results. First, the sample size was relatively small (76 patients), which may have reduced the statistical power to detect differences between groups. Second, the follow-up period varied among participants (4 to 20 months), which could introduce heterogeneity in the observed outcomes. Third, the observational and non-randomized design does not allow for establishing causal relationships between the use of adjuvant medications and the clinical changes observed. Fourth, the lack of standardized data on medication doses and adherence further limits the interpretation of the findings. These factors reinforce the need for future randomized clinical trials with larger samples, standardized follow-up, and detailed treatment information to confirm and expand the evidence presented here. Finally, an important limitation of the present study is the absence of data on adverse events, such as hypoglycemia and urinary tract infections, which are potential effects related to the use of DPP4i and SGLT2i. The database used did not include this information, which made its analysis impossible. Considering that safety is a critical aspect in evaluating the off-label use of these medications in patients with type 1 diabetes, we recommend that future studies include the systematic collection of this data for a better understanding of the associated risk profile. Therefore, the findings of this study should be interpreted with caution and reinforce the need for new studies with larger samples, standardized follow-up, and controlled and randomized design to understand better the effects of DPP4 inhibitors, alone or combined with SGLT2, in individuals with DM1.

It is also important to emphasize that eGFR estimates above 90 mL/min/1.73 m^2 have lower precision, especially in young individuals. However, we chose to maintain the numerical values to allow comparative analyses and ensure methodological consistency, using the CKiD equation validated for this population [14,15]. These values should be interpreted with caution, considering this limitation.

The choice to evaluate DPP-4 and SGLT2 inhibitors in this study reflects real-world clinical practice, where these medications, although off-label, have been used as adjunctive

therapies in young patients with T1DM. In contrast, GLP-1 receptor agonists (GLP-1 RAs), despite their proven cardiovascular, renal, and metabolic benefits in T2DM, are rarely prescribed for children and adolescents with T1DM due to regulatory restrictions, cost, and tolerability concerns. Additionally, DPP-4 inhibitors offer a favorable safety profile and low risk of hypoglycemia, while SGLT2 inhibitors demonstrate potential renal benefits and reduction in glycemic variability. Considering the scarcity of data on these classes in pediatric T1DM populations, observational studies such as the present one are relevant to generate preliminary evidence. Future research should also include GLP-1 RAs to broaden the understanding of adjunctive therapies in this group.

5. Conclusions

The results of this study suggest that the use of DPP4 inhibitors, alone or in combination with SGLT2, did not demonstrate a significant impact on glycemic control, lipid profile, and renal function in children, adolescents, and young adults with type 1 diabetes mellitus during the follow-up period evaluated. However, the significant reduction in albuminuria observed in the group using DPP4 inhibitors alone suggests a possible beneficial effect of these drugs on renal protection, which warrants further exploration in future research. In general, an improvement in glycemic control and lipid profile was observed in the sample as a whole, regardless of the use of medications, which reinforces the fundamental role of interdisciplinary monitoring in the management of DM1. Given the limitations of the present study, it is recommended that randomized clinical trials be conducted with a larger sample size, standardized follow-up, and detailed collection of information related to dose and adherence to treatment to more robustly evaluate the impact of using DPP4 and SGLT2 inhibitors in this population.

6. Future Research

The findings of this study should be interpreted with caution due to its observational design, small sample size, and variable follow-up period. Future research should focus on randomized controlled trials with larger and more diverse populations to confirm the potential renal benefits of DPP-4 inhibitors and clarify their role in glycemic and lipid control in T1DM. Studies should also include standardized follow-up intervals, detailed data on medication doses and adherence, and systematic monitoring of adverse events such as hypoglycemia and urinary infections. Additionally, mechanistic investigations are needed to better understand the pathways through which DPP-4 inhibitors may influence albuminuria and renal outcomes. Comparative studies involving other classes of drugs, such as GLP-1 receptor agonists, would also provide valuable insights into the optimal adjuvant therapy for young individuals with T1DM.

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References

1. Panda, S.P. Role of DPP4 and DPP4i in Glucose Homeostasis and Cardiorenal Syndrome. *Endocr. Metab. Immune Disord. Drug Targets* **2023**, *23*, 179–187. [CrossRef]
2. Akil, A.A.; Yassin, E.; Al-Maraghi, A.; Aliyev, E.; Al-Malki, K.; Fakhro, K.A. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. *J. Transl. Med.* **2021**, *19*, 137. [CrossRef]
3. Deacon, C.F. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **2020**, *16*, 642–653. [CrossRef] [PubMed]
4. Suzuki, Y.; Kaneko, H.; Okada, A.; Komuro, J.; Fujiu, K.; Takeda, N.; Morita, H.; Ako, J.; Nishiyama, A.; Yano, Y.; et al. Comparison of incident hypertension between SGLT2 inhibitors vs. DPP4 inhibitors. *Hypertens. Res.* **2024**, *47*, 1789–1796. [CrossRef]
5. Love, K.M.; Liu, Z. DPP4 Activity, Hyperinsulinemia, and Atherosclerosis. *J. Clin. Endocrinol. Metab.* **2021**, *106*, 1553–1565. [CrossRef]
6. Gong, Y.; Bai, X.; Zhang, D.; Yang, X.; Qin, Z.; Yang, Y.; Zhou, Y.; Meng, J.; Liu, X. Effect of DPP-4i inhibitors on renal function in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis.* **2024**, *23*, 157. [CrossRef]
7. Menegucci, T.; Chagas, E.F.B.; de Oliveira Zanuso, B.; Quesada, K.; Dos Santos Haber, J.F.; Menegucci Zutin, T.L.; Felipe Pimenta, L.; Cressoni Araújo, A.; Landgraf Guiguer, E.; Rucco, P.D.C.; et al. The Influence of Body Fat and Lean Mass on HbA1c and Lipid Profile in Children and Adolescents with Type 1 Diabetes Mellitus. *Diseases* **2023**, *11*, 125. [CrossRef]
8. Keener, A.B. SGLT2 inhibitors breathe life into kidney-disease care. *Nature* **2023**, *615*, S2–S4. [CrossRef] [PubMed]
9. Suzuki, Y.; Kaneko, H.; Okada, A.; Komuro, J.; Ko, T.; Fujiu, K.; Takeda, N.; Morita, H.; Nishiyama, A.; Ieda, M.; et al. Kidney outcomes with SGLT2 inhibitor versus DPP4 inhibitor use in older adults with diabetes. *Nephrol. Dial. Transplant.* **2025**, *40*, 495–504. [CrossRef] [PubMed]
10. Gaggini, M.; Sabatino, L.; Suman, A.F.; Chatzianagnostou, K.; Vassalle, C. Insights into the Roles of GLP-1, DPP-4, and SGLT2 at the Crossroads of Cardiovascular, Renal, and Metabolic Pathophysiology. *Cells* **2025**, *14*, 387. [CrossRef]
11. de Onis, M.; Onyango, A.W.; Borghi, E.; Siyam, A.; Nishida, C.; Siekmann, J. Development of a WHO growth reference for school-aged children and adolescents. *Bull. World Health Organ.* **2007**, *85*, 660–667. [CrossRef]
12. Mancini, M.; Obesidade, D. *Diretrizes Brasileiras de Obesidade 2016, 4.ª edição, Associação Brasileira para o Estudo da Obesidade, Diretoria da ABESO e Editor-Coordenador*; ABESO: São Paulo, Brazil, 2016.
13. Pititto, B.; Dias, M.; Moura, F.; Lamounier, R.; Calliari, S.; Bertoluci, M. Metas no tratamento do diabetes. In *Diretriz Oficial da Sociedade Brasileira de Diabetes*; Conectando Pessoas: Brasília, Brazil, 2022; Volume 2022, pp. 1–23.
14. Pottel, H.; Björk, J.; Delanaye, P.; Nyman, U. Evaluation of the creatinine-based chronic kidney disease in children (under 25 years) equation in healthy children and adolescents. *Pediatr. Nephrol.* **2022**, *37*, 2213–2216. [CrossRef]
15. Gaebe, K.; White, C.A.; Mahmud, F.H.; Scholey, J.W.; Elia, Y.T.; Sochett, E.B.; Cherney, D.Z. Evaluation of novel glomerular filtration rate estimation equations in adolescents and young adults with type 1 diabetes. *J. Diabetes Complicat.* **2022**, *36*, 108081. [CrossRef]
16. Sá, J.; Canani, L.; Rangel, E.; Bauer, A.; Escott, G.; Zelmanovitz, T. Avaliação e tratamento da doença renal do diabetes. In *Diretriz Oficial da Sociedade Brasileira de Diabetes*; Conectando Pessoas: Brasília, Brazil, 2024.
17. Alicic, R.Z.; Cox, E.J.; Neumiller, J.J.; Tuttle, K.R. Incretin drugs in diabetic kidney disease: Biological mechanisms and clinical evidence. *Nat. Rev. Nephrol.* **2021**, *17*, 227–244. [CrossRef]
18. Epelde, F. Impact of DPP-4 Inhibitors in Patients with Diabetes Mellitus and Heart Failure: An In-Depth Review. *Medicina* **2024**, *60*, 1986. [CrossRef]
19. Hoffman, A.F.; Roberson, C.L.; Cohen, P.; Jackson, V.L.; Yeatts, J.; Gregory, P.; Wong, S.; Spratt, S.E. Improving glycemic control in diabetes through virtual interdisciplinary rounds. *Am. J. Manag. Care* **2024**, *30*, e78–e84. [CrossRef]

20. Batir-Marin, D.; Ștefan, C.S.; Boev, M.; Gurău, G.; Popa, G.V.; Matei, M.N.; Ursu, M.; Nechita, A.; Maftei, N.M. A Multidisciplinary Approach of Type 1 Diabetes: The Intersection of Technology, Immunotherapy, and Personalized Medicine. *J. Clin. Med.* **2025**, *14*, 2144. [CrossRef] [PubMed]
21. Scheen, A.J. Reduction in HbA1c with SGLT2 inhibitors vs. DPP-4 inhibitors as add-ons to metformin monotherapy according to baseline HbA1c: A systematic review of randomized controlled trials. *Diabetes Metab.* **2020**, *46*, 186–196. [CrossRef] [PubMed]
22. Saini, K.; Sharma, S.; Khan, Y. DPP-4 inhibitors for treating T2DM—Hype or hope? an analysis based on the current literature. *Front. Mol. Biosci.* **2023**, *10*, 1130625. [CrossRef] [PubMed]
23. Farngren, J.; Persson, M.; Schweizer, A.; Foley, J.E.; Ahrén, B. Vildagliptin reduces glucagon during hyperglycemia and sustains glucagon counterregulation during hypoglycemia in type 1 diabetes. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 3799–3806. [CrossRef]
24. Garg, S.K.; Moser, E.G.; Bode, B.W.; Klaff, L.J.; Hiatt, W.R.; Beatson, C.; Snell-Bergeon, J.K. Effect of sitagliptin on post-prandial glucagon and GLP-1 levels in patients with type 1 diabetes: Investigator-initiated, double-blind, randomized, placebo-controlled trial. *Endocr. Pract.* **2013**, *19*, 19–28. [CrossRef] [PubMed]
25. Foley, J.E.; Ligueros-Saylan, M.; He, Y.L.; Holst, J.J.; Deacon, C.F.; Dunning, B.E.; Leone-Jones, A.; Yu, T.; Kelley, D.E. Effect of vildagliptin on glucagon concentration during meals in patients with type 1 diabetes. *Horm. Metab. Res.* **2008**, *40*, 727–730. [CrossRef]
26. Ellis, S.L.; Moser, E.G.; Snell-Bergeon, J.K.; Rodionova, A.S.; Hazenfield, R.M.; Garg, S.K. Effect of sitagliptin on glucose control in adult patients with Type 1 diabetes: A pilot, double-blind, randomized, crossover trial. *Diabet. Med.* **2011**, *28*, 1176–1181. [CrossRef]
27. Wang, Q.; Long, M.; Qu, H.; Shen, R.; Zhang, R.; Xu, J.; Xiong, X.; Wang, H.; Zheng, H. DPP-4 Inhibitors as Treatments for Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J. Diabetes Res.* **2018**, *2018*, 5308582. [CrossRef] [PubMed]
28. Guo, H.; Fang, C.; Huang, Y.; Pei, Y.; Chen, L.; Hu, J. The efficacy and safety of DPP4 inhibitors in patients with type 1 diabetes: A systematic review and meta-analysis. *Diabetes Res. Clin. Pract.* **2016**, *121*, 184–191. [CrossRef]
29. Pham, T.K.; Nguyen, T.H.T.; Yi, J.M.; Kim, G.S.; Yun, H.R.; Kim, H.K.; Won, J.C. Evogliptin, a DPP-4 inhibitor, prevents diabetic cardiomyopathy by alleviating cardiac lipotoxicity in db/db mice. *Exp. Mol. Med.* **2023**, *55*, 767–778. [CrossRef]
30. Chen, C.Y.; Wu, V.C.; Lin, C.J.; Lin, C.S.; Pan, C.F.; Chen, H.H.; Lin, Y.F.; Huang, T.M.; Chen, L.; Wu, C.J. Improvement in Mortality and End-Stage Renal Disease in Patients with Type 2 Diabetes After Acute Kidney Injury Who Are Prescribed Dipeptidyl Peptidase-4 Inhibitors. *Mayo Clin. Proc.* **2018**, *93*, 1760–1774. [CrossRef]
31. Huang, W.; Chen, Y.-Y.; Li, Z.-Q.; He, F.-F.; Zhang, C. Recent Advances in the Emerging Therapeutic Strategies for Diabetic Kidney Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 10882. [CrossRef]
32. Hasan, A.A.; Hocher, B. Role of soluble and membrane-bound dipeptidyl peptidase-4 in diabetic nephropathy. *J. Mol. Endocrinol.* **2017**, *59*, R1–R10. [CrossRef]
33. Gupta, S.; Sen, U. More than just an enzyme: Dipeptidyl peptidase-4 (DPP-4) and its association with diabetic kidney remodelling. *Pharmacol. Res.* **2019**, *147*, 104391. [CrossRef] [PubMed]