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Does the Efficacy of Semaglutide Treatment Differ between Low-Risk and High-Risk Subgroups of Patients with Type 2 Diabetes and Obesity Based on SCORE2, SCORE2-Diabetes, and ASCVD Calculations?

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Abstract: Background: Diabetes is the primary contributor to cardiovascular disease risk, and when combined with obesity, it further underscores the significance of cardiovascular risk assessment. Methods: A retrospective study of 64 patients with type 2 diabetes (T2D) and obesity on once-weekly subcutaneous semaglutide stratified by cardiovascular risk categories determined using the SCORE2/SCORE2-OP, SCORE2-Diabetes, and ASCVD score calculations. We compare the differences between groups (ASCVD: low + borderline + intermediate versus high-risk group; SCORE2/SCORE2-OP: low + moderate versus high + very high-risk group and SCORE2-Diabetes: low + moderate versus high + very high-risk group) in terms of change from baseline in body mass index (BMI) and HbA1c and weight loss outcomes. Results: Patients in the high-risk group, according to ASCVD risk score, had statistically better results in weight loss $\geq$ 3%, $\geq$5%, and $\geq$10% compared to ASCVD low + borderline + intermediate and without difference regarding HbA1c. According to SCORE2/SCORE2-OP, the high + very high-risk group had statistically better HbA1c and weight loss results but only for $\geq$5% versus the low + moderate risk group. Based on the score SCORE2-Diabetes, the high + very high-risk group had statistically significant better results in lowering HbA1c and weight loss but only for $\geq$5% versus the low + moderate risk group. Conclusions: To the best of our knowledge, this study represents the initial investigation linking glycemic control and weight reduction outcomes in individuals with T2D and obesity treated with once-weekly semaglutide stratified by cardiovascular risk categories determined using the SCORE2/SCORE2-OP, SCORE2-Diabetes and ASCVD score calculations.

Keywords: ASCVD risk score; SCORE2; SCORE2-diabetes; semaglutide; type 2 diabetes; obesity

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1. Introduction

Type 2 diabetes and obesity are global health concerns with increasing prevalence worldwide. Both conditions are associated with a myriad of complications, including cardiovascular diseases, which contribute significantly to morbidity and mortality [1]. This strong association between diabetes and cardiovascular disease is widely acknowledged, with diabetes increasing the risk of coronary artery disease by a factor of two to four [2]. Therefore, it is essential for both healthcare providers and patients with type 2 diabetes (T2D) to undergo a risk assessment using tools such as the ASCVD (atherosclerotic cardiovascular disease) calculator [3] and SCORE2 (Systematic Coronary Risk Evaluation) [4]. The ASCVD Risk estimation is a universally accepted set of guidelines designed to forecast the likelihood of atherosclerotic cardiovascular disease (ASCVD) in individuals. It is employed for patients considered to be at risk of ASCVD. This estimation encompasses several key factors, and essential elements of the risk evaluation include the following: age (validated exclusively for patients aged 40 to 79), gender, total cholesterol levels, HDL cholesterol levels, systolic blood pressure, blood pressure treatment status (yes or no), presence of diabetes mellitus (yes or no), and current smoking status (yes or no) [5]. SCORE2 represents an updated algorithm specifically tailored for European populations, aiming to forecast the 10-year risk of initial cardiovascular disease (CVD) occurrence. This advancement enhances the ability to identify individuals at a heightened risk of developing CVD throughout Europe. The algorithm's development involved the analysis of data from a substantial pool of over 12.5 million individuals across numerous countries. In comparison to SCORE, SCORE2 offers several advantages, as follows: (1) it provides improved estimates of the overall CVD burden, particularly for younger individuals, and demonstrates superior risk discrimination; (2) it factors in the impact of competing risks, including non-CVD-related deaths; (3) it categorizes Europe into four distinct regions with varying CVD risk levels. However, it is important to note that this model has potential limitations. The risk prediction models were primarily derived from 45 cohorts, mainly in European regions and populations with low to moderate CVD risk. Additionally, the model assumes that the relative risks observed in the derivation dataset are applicable across diverse populations [4,6]. The SCORE2-OP risk prediction algorithm serves the purpose of assessing the risk of incident cardiovascular events in individuals aged 70 years or older residing in four distinct geographical risk regions. Most of the existing 10-year cardiovascular disease (CVD) risk prediction models exhibit limited effectiveness when applied to older individuals. SCORE2-OP overcomes this limitation by amalgamating data from three previously established CVD risk algorithms designed specifically for older populations. This model facilitates the estimation of combined outcomes, encompassing both fatal and non-fatal CVD events, and it also enables the calculation of the absolute reduction in CVD risk upon reaching treatment targets for blood pressure and LDL cholesterol. Nonetheless, it is important to acknowledge some potential constraints of this model. Firstly, its development relied on data from a cohort study in a region with low CVD risk. Secondly, certain predictors related to comorbidities or frailty, which might be significant factors in older individuals' CVD risk, were omitted from SCORE2-OP due to data availability constraints [7]. To effectively manage individuals who have both T2D and obesity, it is vital to evaluate each patient's cardiovascular risk. Subsequently, a treatment plan should be developed, and ongoing patient monitoring should be established. Patient monitoring can potentially improve early detection of cardiovascular risk in T2D patients, leading to improved patient outcomes and reduced healthcare costs [8]. Atherosclerotic cardiovascular disease stands as the primary contributor to illness and death among individuals with diabetes, leading to an estimated annual expenditure of USD 37.3 billion on diabetes-related cardiovascular care. On average, individuals with a confirmed diabetes diagnosis incur medical costs that are approximately 2.3 times greater than their expenses if they do not have diabetes [9–11]. The American Heart Association has advocated for the adoption of preventive measures, emphasizing the importance of addressing obesity in order to alleviate the impact of heart disease [9,10]. Presently, the American Diabetes Association (ADA) guidelines recommend

using the ASCVD Risk Estimator Plus tool to assess the initial 10-year cardiovascular risk of experiencing ASCVD events [3,10].

Recently, a newly developed algorithm called SCORE2-diabetes underwent calibration and validation in four European regions to forecast the 10-year risk of CVD in individuals with T2D. This innovative tool incorporates diabetes-specific variables, including the age at diabetes diagnosis, glycated hemoglobin (HbA1c), and the estimated glomerular filtration rate (eGFR), in addition to traditional risk factors [12]. The validation of SCORE2-Diabetes in four distinct European countries, each representing diverse risk regions. The validation of SCORE2-Diabetes across four European countries (Croatia, Malta, Spain, and Sweden) from different risk regions demonstrated the model's precision in forecasting the cardiovascular disease risk linked with type 2 diabetes, both on an individual and population-wide basis [12].

As a GLP-1 receptor agonist, semaglutide enhances the efficiency of GLP-1 through diverse mechanisms, including enhanced glucose-dependent insulin secretion, inhibition of glucagon release, and suppressed hepatic gluconeogenesis [13]. As a result of these multiple effects, semaglutide contributes to decreased levels of fasting and postprandial glycemia, along with a reduction in food energy intake and delay in gastric, ultimately leading to weight loss [13].

Therefore, lowering both HbA1c levels and body weight without the risk of hypoglycemia gives it a distinct status in the treatment of individuals with obesity and type 2 diabetes [14].

Semaglutide, an FDA and EMA-approved GLP-1 receptor agonist for managing type 2 diabetes, has demonstrated statistically significant reductions in cardiovascular events [13]. Additionally, semaglutide was registered with the same regulatory authorities but at a higher dose of 2.4 mg once weekly subcutaneously for the treatment of obesity as an addition to behavioral therapy [15–17].

Existing models for predicting CVD risk in primary prevention settings may have notable limitations, especially when applied to patients with both T2D and obesity. This study aims to ascertain whether there are variations in the effectiveness of semaglutide treatment in terms of glycemic control and weight loss between subgroups of low-risk and high-risk patients with type 2 diabetes and obesity, determined through ASCVD score, SCORE 2/SCORE2-OP, and SCORE2-Diabetes calculations.

2. Patients and Methods

This was a retrospective study of patients with T2D and obesity who were treated using an individual approach in ambulatory in University Hospital Centre Zagreb at Department of Endocrinology. This study analyzed patients receiving once-weekly subcutaneous semaglutide (Ozempic®) for glycemia regulation. Patients who reached a semaglutide dose of $\geq$0.5 mg (before ambulatory control endpoint assessment at 6–8 months post introduction) and had all the variables needed for SCORE2/SCORE2-OP, SCORE2-Diabetes, and ASCVD risk calculation were included in our study [methodology and principle extensively presented in Refs. [3,6].

All relevant demographic (age, gender, and race) and clinical [height, body weight (BW), body mass index (BMI), HbA1c, fasting glucose, presence of comorbidities (arterial hypertension, dyslipidemia, and hypothyroidism), as well as other variables needed for SCORE2/SCORE2-OP, SCORE2-Diabetes and ASCVD risk calculation (e.g., systolic blood pressure, total cholesterol and HDL cholesterol, smoking status, data on using antihypertensives and statins in chronic pharmacotherapy, duration of diabetes, eGFR)] were collected.

The standard principles of T2D and obesity care (assessments and follow-up, e.g., methodology and principles and cut-offs for measurements for all studied anthropometric and biochemical parameters as well for blood pressure measurement) within the Croatian Referral Center for Obesity Treatment (which is also EASO collaborating center for obesity

management), which are the same methodology principles applied here, were recently extensively presented and published elsewhere [18].

SCORE2/SCORE-OP, SCORE2-Diabetes and ASCVD cardiovascular risk categories were calculated for each patient as per standardized and validated principles published by the European Society of Cardiology [extensively presented in Refs. [3,6,12].

Patients were divided into SCORE2/SCORE2-OP low + moderate (SCORE2 group 1) and SCORE2/SCORE2-OP high + very high-risk (SCORE2 group 2) groups, SCORE2-Diabetes low + moderate (SCORE2-Diabetes group 1) and SCORE2-Diabetes high + very high-risk (SCORE2-Diabetes group 2), as well as ASCVD low + borderline + intermediate (ASCVD group 1) and ASCVD high-risk (ASCVD group 2) groups in order to compare the results of semaglutide weight loss- and glycemia regulation-wise, depending on the baseline cardiovascular risk as a potential therapy effectiveness predictor.

Studied endpoints were changes in body weight ($\triangle$BMI, and $\triangle BW \geq 3\%$, $\triangle BW \geq 5\%$, and $\triangle BW \geq 10\%$ percentage of patients) and glycemia ($\triangle$HbA1c) at the ambulatory check-up 6–8 months after the initiation of the once-weekly subcutaneous semaglutide (Ozempic®).

The study was approved by the local Ethics Committee of the University Hospital Centre Zagreb, Croatia. Bearing in mind the retrospective nature of the study and its design, as well as the fact that the used data had been anonymized and already recorded, a waiver of informed consent was approved (Permit class: 8.1-18/161-2, No. 02/21 AG). Overall, the study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel version 2311 (Microsoft Office, Redmond, WA, USA) and MedCalc v14.8.1 (MedCalc Software bvba, Ostend, Belgium) and Python (v3.9.10). Absolute and relative frequencies, measures of central tendency alongside measures of spread, were used to present the data. The Kolmogorov–Smirnov test was used to assess the normality of distribution. Mann–Whitney test was used to compare the differences between groups (ASCVD: low + borderline + intermediate versus high-risk group; SCORE2: low + moderate versus high + very high-risk group, and SCORE2-Diabetes: low + moderate versus high + very high-risk group) in terms of change from baseline in BMI and HbA1c. Furthermore, to compare the differences (frequencies of patients) in other weight loss outcomes ($\triangle BW \geq 3\%$, $\triangle BW \geq 5\%$, and $\triangle BW \geq 10\%$), a $\chi 2$-test was used. All statistical tests were two-tailed and with a 95% CI. Overall, the criterion for statistical significance was set at $p < 0.05$.

3. Results

Overall, 64 patients [60.9% female; median age 57.5 (41–81) yr.] on once-weekly subcutaneous semaglutide meet our enrolment criteria. The vast majority of patients were severely obese and had a high cardiovascular risk (Table 1).

Comparison between subgroups (SCORE2 low + moderate vs. SCORE2 high + very high-risk group; SCORE2-Diabetes low + medium vs. SCORE2-Diabetes high + very high-risk group, and ASCVD low + borderline + intermediate vs. ASCVD high-risk group, with Mann–Whitney test) in terms of baseline BW, BMI, and HbA1c revealed the following: 131.1 ± 31.2 kg vs. 114.8 ± 23.6 kg ($p = 0.064$); 132.3 ± 30.4 vs. 119.1 ± 24.6 kg ($p = 0.148$), and 123.5 ± 28.7 kg vs. 113.9 ± 23.7 kg ($p = 0.290$); 46.6 ± 10.6 kg/m^2 vs. 40.4 ± 6.4 kg/m^2 ($p = 0.017$), 46.9 ± 10.9 vs. 41.7 ± 6.5 kg/m^2 ($p = 0.101$), and 43.6 ± 8.9 kg/m^2 vs. 40.2 ± 7.4 kg/m^2 ($p = 0.097$); $6.7 \pm 1.0\%$ vs. $7.5 \pm 1.3\%$ ($p = 0.018$), $6.6 \pm 0.9\%$ vs. $7.4 \pm 1.4\%$ ($p = 0.022$), and $6.9 \pm 1.2\%$ vs. $7.8 \pm 1.2\%$ ($p = 0.003$), respectively.

Table 1. Demographic and baseline clinical characteristics of our T2D cohort (N = 64) using subcutaneous semaglutide once-weekly.

Gender distribution (%, N of female patients)		60.9%, 39
Age (Median, Min-Max, yr.)		57.5 (41–81)
Height (X ± SD, cm)		168.1 ± 10.1
Weight (X ± SD, kg)		120.4 ± 27.3
BMI (X ± SD, kg/m^2)		42.5 ± 8.5
BMI category distribution (%, N)	BMI < 25 kg/m^2	0%, 0
	Overweight	0%, 0
	Obesity class I	14.1%, 9
	Obesity class II	31.3%, 20
	Obesity class III	54.7%, 35
Comorbidities (%, N)	Arterial hypertension	79.7%, 51
	Dyslipidemia	84.4%, 54
	Hypothyroidism [1]	17.2%, 11
HbA1c (X ± SD, %)		7.2 ± 1.3
Fasting glucose (X ± SD, mmol/L)		8.6 ± 2.2
Semaglutide dose achieved (%, N)	0.5 mg	60.9%, 39
	1 mg	39.1%, 25
SCORE2 distribution (%, N)	Low	0%, 0
	Moderate	34.4%, 22
	High	43.7%, 28
	Very high	21.9%, 14
SCORE2-Diabetes distribution (%, N) [2]	Low	10.5%, 6
	Moderate	22.8%, 13
	High	42.1%, 24
	Very high	24.6%, 14
ASCVD distribution (%, N)	Low	15.6%, 10
	Borderline	14.1%, 9
	Intermediate	37.5%, 24
	High	32.8%, 21

[1] All patients were euthyroid during the study follow-up period, [2] Sample size = 57 patients.

Results of the Statistical Analysis

SCORE 2 high + very high-risk group had statistically better results in terms of △BMI (−2.4 ± 2.1 kg/m^2 vs. −1.3 ± 1.5 kg/m^2, p = 0.045; Figure 1) and △HbA1c (−0.9 ± 1.2% vs. −0.2 ± 0.9%, p = 0.013; Figure 2) as well as the frequency of patients who achieved △BW ≥ 5% (61.9% vs. 22.7%, X^2 = 8.744, p = 0.003), when compared to SCORE2 low + medium group. Not statistically significant differences between groups were revealed in terms of △BW ≥ 3% (73.8% vs. 54.5%, X^2 = 2.400, p = 0.121) and △BW ≥ 10% (21.4% vs. 4.5%, X^2 = 3.084, p = 0.079) frequencies.

SCORE2-Diabetes high + very high (N = 38) risk group, when compared to SCORE2-Diabetes low + medium (N = 19), had statistically better results in terms of △BMI (−2.4 ± 2.0 kg/m^2 vs. −1.1 ± 1.6 kg/m^2, p = 0.039; Figure 3), △BW ≥ 5% (57.9% vs. 21.0%, X^2 = 6.831, p = 0.009), and △HbA1c (−0.9 ± 1.2% vs. −0.2 ± 0.9%, p = 0.028; Figure 4). However, no statistically significant difference was found in terms of △BW ≥ 3%

(73.7% vs. 47.4%, $X^2 = 3.780$, $p = 0.052$) and △BW ≥ 10% (18.4% vs. 5.3%, $X^2 = 1.770$, $p = 0.183$).

The ASCVD high (N = 21) risk group had statistically better results in terms of all studied anthropometric/weight loss endpoints compared to ASCVD low + borderline + intermediate risk group (N = 43): △BMI (-2.8 ± 1.9 kg/m^2 vs. -1.7 ± 1.9 kg/m^2, $p = 0.030$; Figure 5), and △BW ≥ 3% (85.7% vs. 58.1%, $X^2 = 4.797$, $p = 0.028$), △BW ≥ 5% (71.4% vs. 37.2%, $X^2 = 6.504$, $p = 0.011$), and △BW ≥ 10% (28.6% vs. 9.3%, $X^2 = 3.923$, $p = 0.048$) frequencies. No difference was found regarding △HbA1c (-1.2 ± 1.1% vs. -0.4 ± 1.1%, $p = 0.591$; Figure 6).

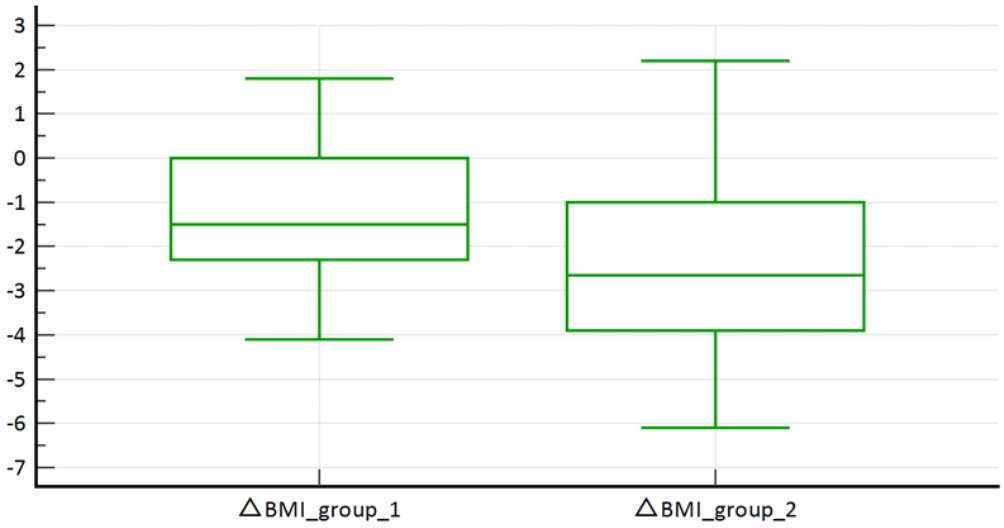

Figure 1. Comparison between SCORE2 low + medium (below SCORE2 group 1) vs. SCORE 2 high + very high-risk (above SCORE2 group 2) groups in terms of △BMI.

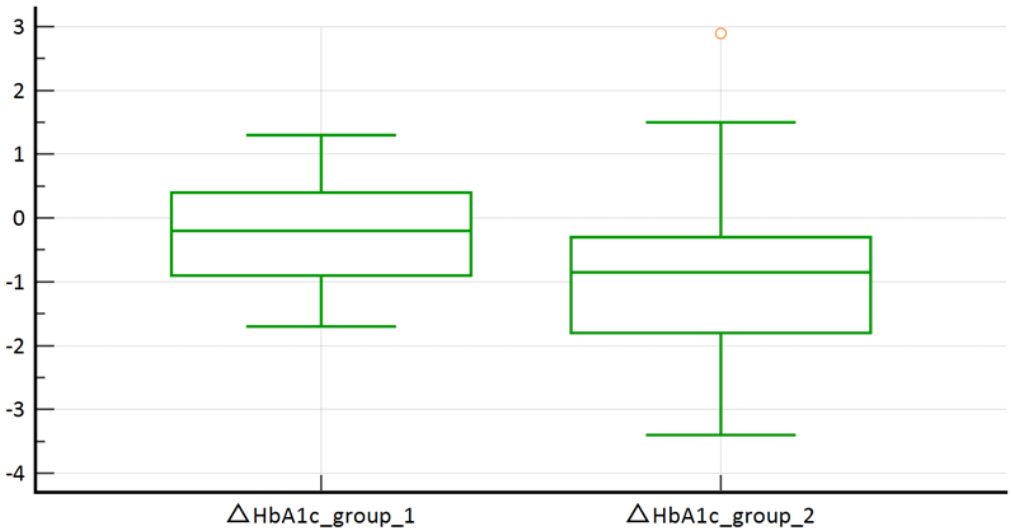

Figure 2. Comparison between SCORE2-Diabetes low + medium (above SCORE2-Diabetes group 1) vs. SCORE2-Diabetes high + very high risk (below SCORE2-Diabetes group 2) groups in terms of △BMI.

Additionally, the use of other medication was inspected prior to semaglutide therapy.

Patients previously treated with SGLT2 inhibitors (N = 13) demonstrated a less pronounced reduction in BMI, with a mean change of -1.06 ± 2.09 kg/m^2, compared to a mean reduction of -2.28 ± 1.85 kg/m^2 in the untreated group (N = 51). This difference was statistically significant (U-value: 458.5, $p = 0.017353$), indicating a lesser degree of BMI reduction in the SGLT2 inhibitor-treated group (Figure 7).

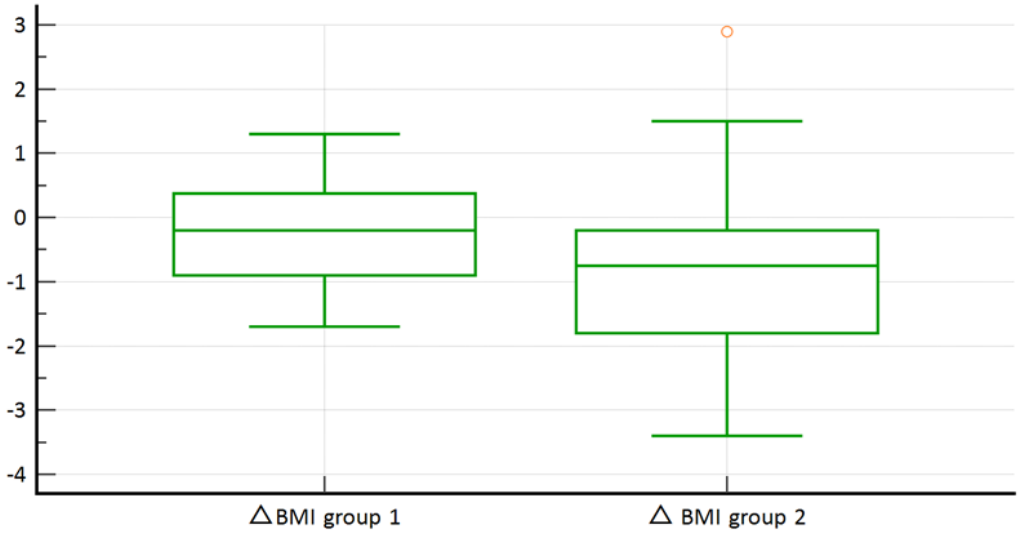

Figure 3. Comparison between SCORE2-Diabetes low + medium (above SCORE2-Diabetes group 1) vs. SCORE2-Diabetes high + very high-risk (below SCORE2-Diabetes group 2) groups in terms of △BMI.

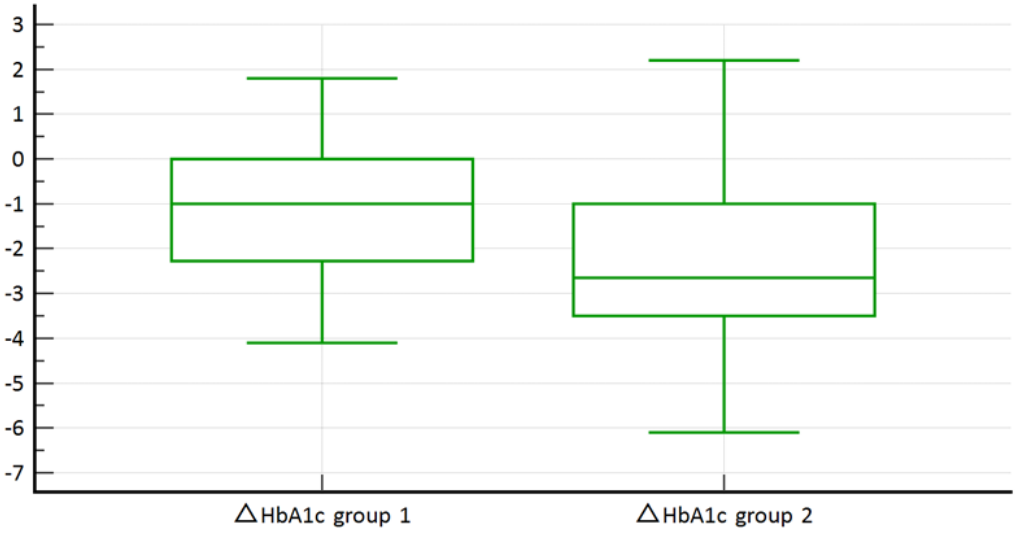

Figure 4. Comparison between SCORE2-Diabetes low + medium (above SCORE2-Diabetes group 1) vs. SCORE2-Diabetes high + very high-risk (below SCORE2-Diabetes group 2) groups in terms of △HbA1c.

In the comparison of delta HbA1c% levels, the group treated with SGLT2 inhibitors (N = 13) showed a mean reduction of $-0.41 \pm 1.34\%$, which was less than the $-0.72 \pm 1.09\%$ observed in the untreated group (N = 51). The statistical analysis yielded a U-value of 416.5 and a *p*-value of 0.079177, suggesting a trend towards a lesser reduction in HbA1c% among the SGLT2 inhibitor-treated patients, although this did not reach conventional levels of statistical significance (Figure 7).

Figure 8 shows that there is no significant difference in the intake of SGLT-2 inhibitors, concerning age, BMI, weight or the three scores. A Mann–Whitney U test confirmed this.

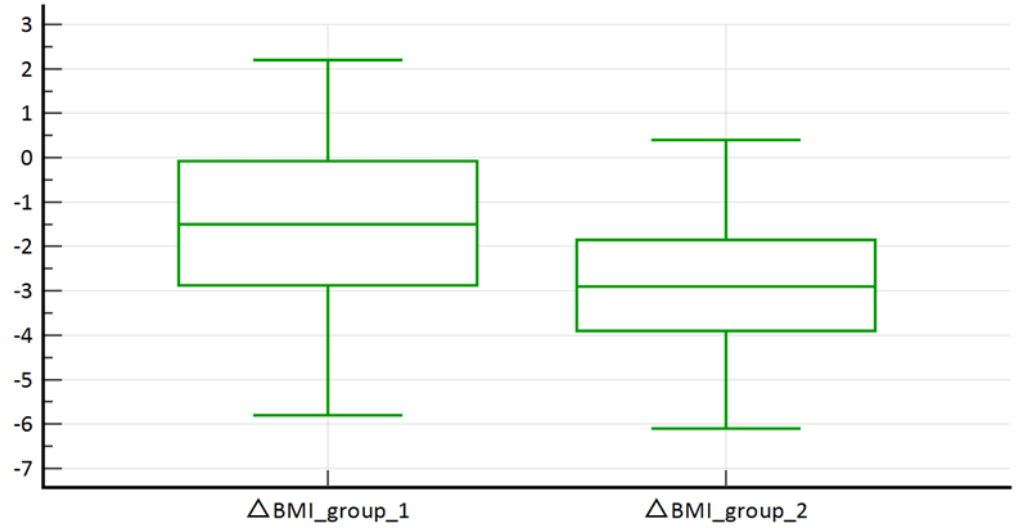

Figure 5. Comparison between ASCVD low + borderline + intermediate (above SCORE2 group 1) vs. ASCVD high risk (below SCORE2 group 2) groups in terms of △BMI.

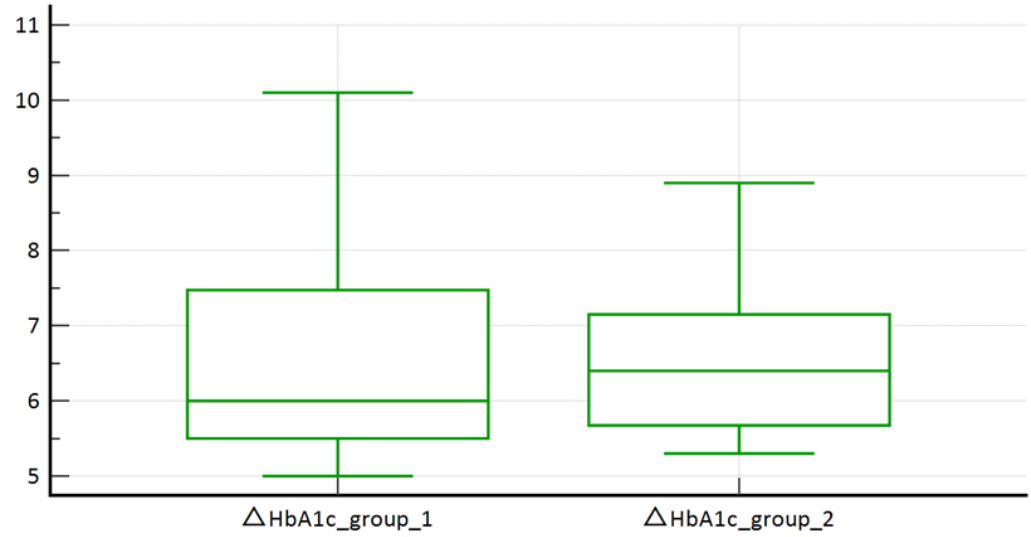

Figure 6. Comparison between ASCVD low + borderline + intermediate (below SCORE2 group 1) vs. ASCVD high risk (above SCORE2 group 2) groups in terms of △HbA1c.

For patients treated with other GLP-1 agonists (N = 18), the mean reduction in BMI was -1.29 ± 1.82 kg/m^2, compared to a more substantial mean reduction of -2.33 ± 1.93 kg/m^2 in the non-treated group (N = 46). This difference was statistically significant (U-value: 567.0, $p = 0.011361$), indicating a greater reduction in BMI among patients not treated with GLP-1 agonists.

Regarding the change in HbA1c% levels, patients treated with other GLP-1 agonists (N = 18) experienced a mean reduction of -0.41 ± 1.37%, in contrast to a mean reduction of -0.76 ± 1.03% in the non-treated group (N = 46). The statistical analysis showed a U-value of 518.5 and a p-value of 0.060143, indicating a trend towards a lesser reduction in HbA1c% in the GLP-1 agonist-treated group, though not reaching a level of statistical significance.

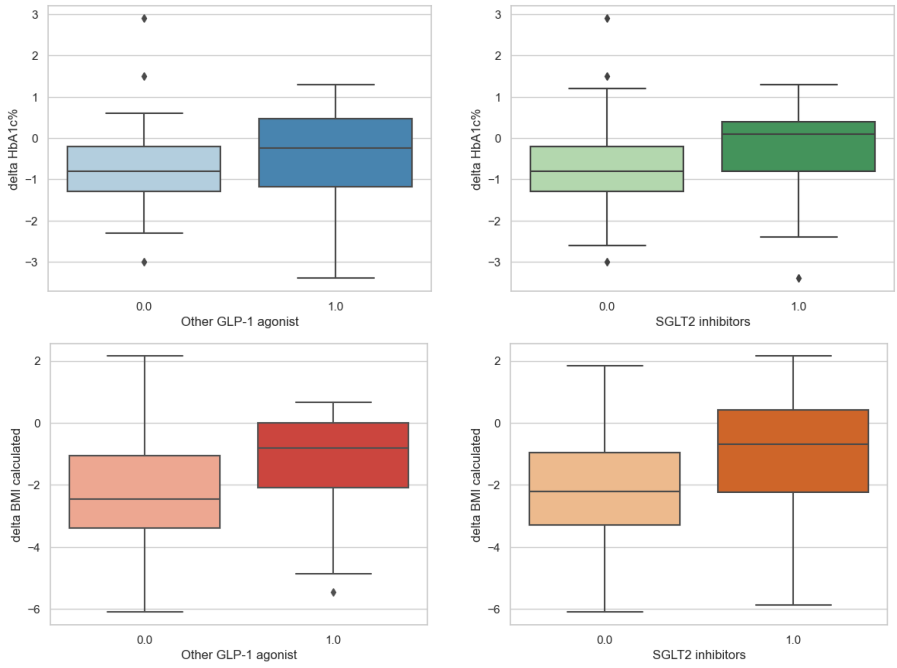

Figure 7. Comparison between patient who took Other GLP-1 agonists (**left** side) and SGL2 inhibitors (**right** side) groups in terms of △HbA1c (**top**) and △BMI (**bottom**).

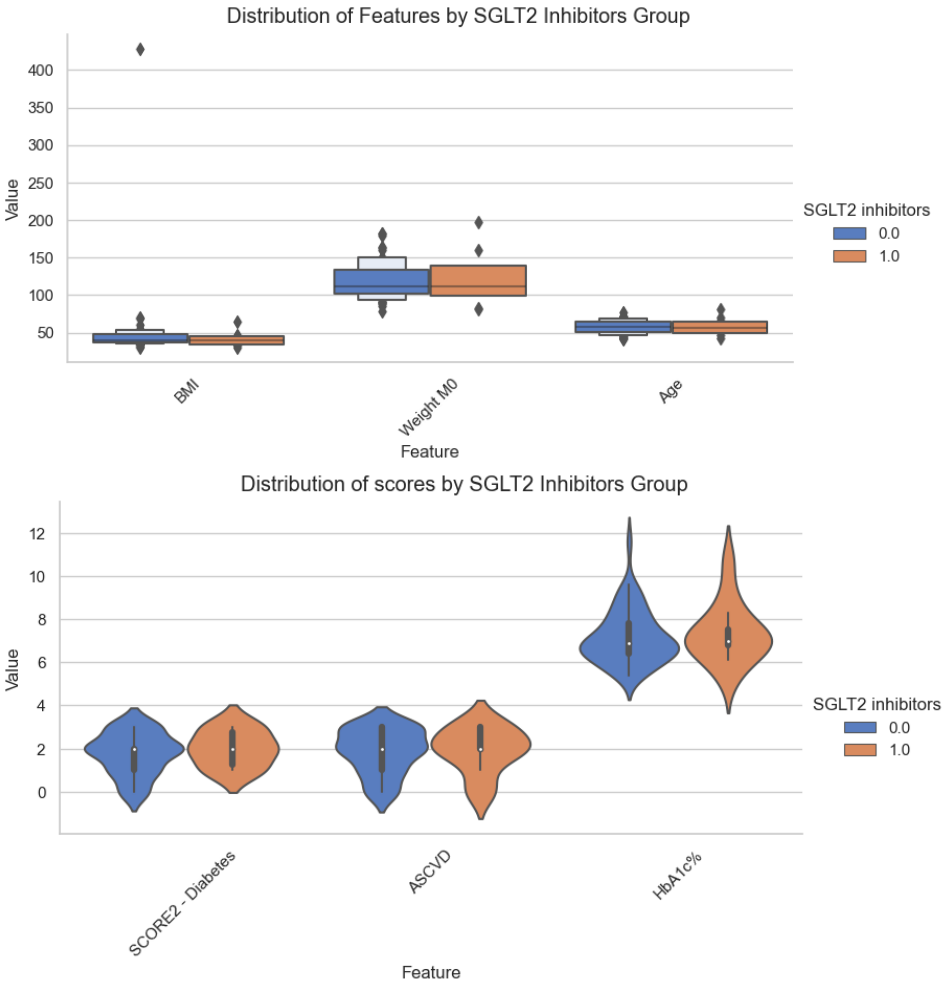

Figure 8. Differences in age and anthropometry in the groups of patients on SGLT2 inhibitors (1) and those who are not (0) in the upper figure, while the lower figure shows differences in the score.

4. Discussion

Mitigating cardiovascular risk holds significant importance in lowering morbidity rates among individuals with diabetes. This significance is amplified in patients who are concurrently dealing with both diabetes and obesity.

Selecting medications that effectively lower glucose levels, promote weight loss, and enhance cardiovascular outcomes is crucial for individuals dealing with both type 2 diabetes and obesity. The central message is that both categories of medications, including GLP-1 receptor agonists and SGLT2 inhibitors, have demonstrated their effectiveness in "proven cardiovascular efficacy". Semaglutide is one of the medications that showed these characteristics [19]. Noteworthy, obesity can double CVD risk in all patients with type 2 diabetes [20].

The SCORE 2/SCORE 2- OP high and very high-risk group showed statistically significant improvements in terms of reducing BMI and HbA1c levels, as well as a higher proportion of patients achieving weight loss $\geq$ 5% compared to the SCORE 2 low and moderate-risk group. There were not statistically significant differences between the two groups in terms of weight loss $\geq$ 3% and weight loss $\geq$ 10% achievement rates.

In the SUSTAIN-6 study, in patients with type 2 diabetes and with established cardiovascular disease, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was shown to be significantly lower among patients receiving semaglutide than among those receiving placebo [13]. In this study, by week 104, patients treated with semaglutide experienced notable improvements when compared to those receiving a placebo. Specifically, their average glycated hemoglobin levels decreased from 8.7% at the beginning of the study to 7.6% (for the group receiving 0.5 mg) and 7.3% (for the group receiving 1.0 mg). Additionally, the mean body weight of patients receiving semaglutide decreased from an initial 92.1 kg to 88.5 kg (for the 0.5 mg group) and 87.2 kg (for the 1.0 mg group) [13].

In our study, the average glycated hemoglobin levels of participants (for the 0.5 mg and 1 mg groups) decreased from 7.2% initially to 6.5%. Additionally, patients receiving semaglutide experienced a reduction in mean body weight from 120.4 kg to 113.8 kg and a decrease in BMI from 42.5 kg/m^2 to 40.4 kg/m^2. In comparison to the SUSTAIN-6 study lasting 104 weeks, our study, conducted over 26 to 34 weeks, showed lower baseline HbA1c but higher baseline body weight and BMI, with a smaller drop in HbA1c and a greater reduction in body weight and BMI. This preliminary comparison highlights the need for an extended study duration to draw more meaningful conclusions.

These outcomes can be elucidated by the previously established mechanisms of action of semaglutide on glucose, HbA1c, and body weight [13].

In these cardiovascular outcomes trials, patients treated with semaglutide exhibited a significant 26% reduction in the risk of the primary composite outcome when compared to those receiving a placebo [13]. This risk reduction was primarily driven by a significant 39% decrease in nonfatal stroke rates and a nonsignificant 26% decrease in nonfatal myocardial infarction, with no significant difference in cardiovascular death rates. These risk reductions were consistent across both doses of semaglutide [13]. The SUSTAIN-6 and PIONEER-6 studies demonstrate the positive impact of semaglutide on reducing cardiovascular risk and post hoc analysis revealed approximately a 24% reduction in cardiovascular adverse events compared to the placebo [21].

Both the 0.5 mg and 1.0 mg doses of semaglutide demonstrate significant enhancements in glycemic management and body weight reduction in individuals with type 2 diabetes vs. comparators, irrespective of whether they are concurrently using other antidiabetic medications [22–24].

In our research, the exclusion criterion was a history of established CVD, which includes previous cardiovascular, cerebrovascular, or peripheral vascular diseases. However, we observed that those at high-risk (high and very high-risk group), as determined by the SCORE2/SCORE2-OP calculation, experienced more significant improvements in lowering HbA1c and reducing body weight in terms of a weight loss $\geq$ 5% versus the low-risk

group (low and moderate). Nevertheless, our observations indicated that individuals in the high-risk category (comprising the high and very high-risk groups), as determined by the SCORE2/SCORE2-OP calculation, demonstrated more substantial enhancements in reducing HbA1c levels and weight loss $\geq$ 5% compared to the low-risk group (consisting of the low and moderate-risk individuals). However, there were no discernible differences between groups regarding weight loss $\geq$ 3% and $\geq$10%.

Patients with T2D on semaglutide in our study had a higher body mass index (BMI) and better glycemic control, reflected in lower average HbA1c levels, compared to patients in the SUSTAIN-6 study who received semaglutide.

The SCORE2-Diabetes algorithms were recently developed by extending SCORE2, using data from >220,000 patients with T2D with good external validation in >210.000 individuals from four countries, including Croatia [12]. However, similar outcomes in our study (weight loss $\geq$ 5% and decreasing HbA1c) were in the risk group patients calculated via the SCORE2/SCORE2-OP and SCORE-Diabetes. It is possible that even more substantial changes could be observed if the observation period were extended.

Across all BMI subgroups, the individual SUSTAIN 1 to 5 trials [22–26] demonstrated that semaglutide resulted in significantly higher percentages of subjects achieving weight loss of $\geq$5% and $\geq$10% compared to the comparator groups, with a more pronounced effect observed with the 1.0 mg dose of semaglutide compared to the 0.5 mg dose. We demonstrated that individuals with type 2 diabetes and obesity who received once-weekly semaglutide treatment achieved significant weight loss ($\geq$3%, $\geq$5%, and $\geq$10%) in the high-risk group compared to the lower-risk group (comprising those with low, borderline, and intermediate risk) according to the ASCVD score although the initial BMI was lower in the high-risk group. However, there was no significant difference in terms of HbA1c reduction between these two groups.

Although other CVD risk prediction scores are recommended in patients with diabetes, the prediction of CVD via the SCORE system was significantly better than, for example, the UK Prospective Diabetes Study System [27]. The incorporation of diabetes as a categorical variable in the SCORE equation quadruples the CVD risk for diabetic women and doubles it for diabetic men. This equation does not consider the glycemic control or diabetes duration, which can under- or overestimate real CVD risk [28]. Because of its similarity, these limitations can also be applied to SCORE2 risk. Zhang et al. suggested that HbA1c values should be used in CVD risk assessment, especially in patients with HbA1c of 7–8% and low or moderate ASCVD score risk [29]. SCORE 2 and ASCVD risk are relatively new CVD risk assessment methods, and there are no scientific studies investigating the benefit of semaglutide in patients with lower or higher CVD risk assessed by them.

Patients with both type 2 diabetes and obesity, deemed at high risk based on the above score calculations, attained more favorable outcomes. These results can be partially attributed to our multidisciplinary approach comprising an endocrinologist-diabetologist, nutritionist, psychiatrist, psychologist, cardiologist, nephrologist, and neurologist for the treatment of individuals with obesity and/or T2D, aligning with the guidelines provided by the ADA guidelines [10,30]. Since patients with obesity and diabetes mellitus represent a great challenge, both in treatment, which does not only include pharmacotherapy but also a change in lifestyle is very important in order to achieve satisfactory results of treatment and control of the disease. Furthermore, the very use of any drug that is related to weight loss calls into question one's own active role in terms of whether something happens because of that medication or because of one's own behavior, which calls into question one's own motivation and requires a certain level of adaptation to the situation itself and direction of behavior. Mobile applications that can be used to quickly and easily monitor caloric intake and body wight and encourage exercise certainly play an interesting role [31,32]. Awareness of the problem of obesity can certainly be one of the focuses and therapeutic goals in psychotherapy, and an integrative approach that, together with an endocrinologist who deals specifically with obesity, together with a psychologist and a psychiatrist, can certainly help more than without psychological support [30,33]. An existing aspect among

some of our patients includes pre-existing psychological conditions that can adversely affect individuals with diabetes in general. These conditions can influence factors such as motivation, self-care behaviors, glucose control, and medication adherence, all of which play a significant role in diabetes management. It is, therefore, important to pay attention to these psychological barriers as a vital step in enhancing diabetes care and addressing the individual challenges posed by this disease [34].

Equally, in today's world, there is mostly an insistence on instant solutions, fast diets that can quickly lose body weight, but most contemporary research claims that there is no universally successful diet, from the Mediterranean to intermittent fasting [35–38].

The analysis of medication use revealed that patients previously treated with SGLT2 inhibitors exhibited a significantly lesser reduction in BMI compared to those not treated with these inhibitors. However, the difference in HbA1c% reduction between the treated and untreated groups, although trending towards lesser reduction in the treated group, did not reach statistical significance. Similarly, patients treated with other GLP-1 agonists showed a lesser reduction in both BMI and HbA1c% compared to their untreated counterparts, with the difference in BMI being statistically significant. These findings suggest that prior treatment with SGLT2 inhibitors and other GLP-1 agonists may influence the effectiveness of interventions aimed at reducing BMI and HbA1c% levels.

5. Limitations

None of the scoring systems (ASCVD, SCORE2/SCORE-OP, and SCORE-Diabetes) incorporate BMI as an element within the cardiovascular risk assessment algorithm. In forthcoming research, it is recommended to involve a greater number of patients with diabetes and obesity class 2 and 3 for comparison with individuals of normal body weight or those who are overweight to see if there is a difference in the 10-year prediction of CVD according to BMI.

The sample size for this study is relatively small, so in the future, a larger sample size would enhance the study's robustness and generalizability. Additionally, in the future investigation, it would be preferable to ensure a more balanced representation among the stratified risk groups.

6. Conclusions

The effectiveness of semaglutide therapy in individuals with type 2 diabetes and obesity was confirmed in those categorized as high-risk according to ASCVD calculations, as well as according to SCORE/SCORE2-OP and SCORE-Diabetes assessments. Patients with higher risk experienced more substantial improvements in glycemic control, resulting in lower HbA1c levels and weight reduction, even though they initially had a lower BMI when they began treatment. Further research is necessary to expand the study population, encompassing individuals with both diabetes and obesity, as well as those without obesity who received weekly subcutaneous semaglutide. This research assessed the variations in treatment effectiveness between these groups based on their ASCVD, SCORE2/SCORE-OP, and SCORE2-Diabetes risk assessments.

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