In 94 of the 100 patients enrolled it was possible to conclude the analysis, detecting the glycaemic variability, the point glycaemia values and the estimated glycated haemoglobin value. A glycaemia ≥200 mg/dL was found in 53 patients (56%) while a high glycaemic variability was found in 51 patients (54%). A blood glucose value <59 mg/dL was found in 48 patients (51%). Only 5 times the estimated glycated Hb values were < 7%. 32 of the patients who had at least 3 punctual glucose values ≥200 mg/dL were prescribed an oral glucose load curve, which in 100% of cases confirmed the diagnosis of diabetes. No statistically significant differences were found based on age group or sex. In the control group, consisting of 10 patients without DHF undergoing continuous glucose monitoring at one of the participating cardiology units, an unknown hyperglycaemia was found in only 1 patient.
(10%) and a glycaemic variability in only 1 patient (10%).

1.5. Conclusions: Our experience suggests an incidence of hyperglycaemia and glycaemic variability more than 65% in patients affected by HFpEF. If our data were reproducible on a large scale, a so high prevalence of diabetes in patients with HFpEF cold explain the efficacy of SGLT-2 inhibitor and GLP-1 Agonist in this class of patients.

2. Introduction

Heart failure patients with preserved ejection fraction (HFpEF) is estimated to represents approximately 50% of all Hearth Failure (HF) cases [1, 2]. HFpEF is a heterogeneous syndrome, with several underlying etiologic and pathophysiologic factors. The prevalence of this syndrome continues to increase in the developed world, likely because of the increasing prevalence of common risk factors, including older age, female sex, hypertension, diabetes, renal dysfunction, and obesity [3, 4]. Consequently, HFPEF might become the prevalent phenotype of heart HF in the coming decades. HFpEF is characterized by the presence of dysfunction of the left ventricle, which manifests itself with the prolongation of the isovolumetric relaxation phase, with the reduction of the diastolic filling speed and with the increase of the diastolic filling time, all associated with the increase the stiffness of the ventricular wall [5]. Although diabetes is a major cause of HFpEF and is associated with a worse prognosis in patients with HFpEF [6], the role of Glycemic Variability (GV) remains unknown, especially in non-diabetic patients. In these patients the GV might identify a particular phenotype with important therapeutic implications.

3. Materials and Methods

3.1. Study Design

One hundred general practitioners (GPs) participated in the study during October - December 2021: 245 patients, afferent for a generic consultation, completed a preliminary cardiologic screening, 111 reported chronic heart failure symptoms and an echocardigram with HFpEF pattern; of these 100 accepted and completed all the procedures. The procedures of the study including an evaluation of a serological of glycemic pattern, comorbidities evaluation, smoking habits, Body Mass Index, general symptoms, and glycemic holter.

3.2. Procedures

The glycemic holter device has a 14-day real-time glucose oxidase electrochemical sensor with a soft flexible sensor probe. When the sensor probe invades the subcutaneous tissue, glucose and oxygen in the interstitial fluid permeate into the sensor probe, and an electrochemical reaction occurs to generate an electrical signal. This signal is processed by a transmitter (7 mm thickness and 3 years of usage life) that sends data of interstitial glucose levels every 3 min, an applicator to apply the transmitter with a single click, and software to store and share data. The applicator was designed to be simple to use and features a button that positions the sensor in place and retracts the introducer needle when pressed.

The electric signal processed by the transmitter is converted to blood glucose reading and transmitted to the mobile application through Bluetooth. The application displays the blood glucose reading in real time, reflects the fluctuation trend of blood glucose and generates the trend curve, and can export the historical data. Participants were trained to use the system. All sensors were inserted at the clinic using the automated sensor applicator on the abdomen.

Two sensors were inserted in each participant for better performance evaluation. After 7 days of wear-in period, paired continuous blood glucose values and venous blood glucose values were collected for each participant [5].

3.3. Comorbidities

The most common chronic comorbidities were Metabolic disorders (i.e., hypertryglceridemia, Hypercholesterolemia), Cardiovascular diseases (i.e., cardiopathy, atrial fibrillation, arrhythmia, IMA), Hypertension, mental health disorders (i.e., depression, anxiety), Respiratory diseases (i.e., COPD, asthma, OSAS, Bronchiectasis), Allergy, Diseases of the musculoskeletal system (i.e., osteoporosis, arthropathy, low back pain), Obesity, Gastrointestinal disease (i.e., gastritis, colitis, hiatal hernia), Thyroidopathy, Other. Number of comorbidities was evaluated as the sum of all the comorbidities of each patient.

3.4. Data Analysis

Statistical analyses were performed in SPSS version 20. Prevalence and measures of central tendency were used to describe the anthropometric and clinical data. Doctor diagnoses were compared with patient reports and spirometric categories. Associations with diagnosis were assessed with Fisher's exact tests. p values <0.05 were considered statistically significant. Logistic regression analysis was performed to analyze the relationships between the study variables.

4. Results

100 patients with HFpEF admitted to cardiology units of 4 Italian centres on the major islands were enrolled consecutively. Gluno-vo® was applied to each enrolled patient for 7 days, taking a total of 3360 punctual glucose measurements for each patient in the abdominal interstitial fluid. The HFpEF diagnosis required three obligatory conditions had to be simultaneously satisfied: presence of signs or symptoms of congestive heart failure; presence left ventricular systolic function >55%; evidence of abnormal relaxation pattern of transmitral flow and an increased E/E’ ratio in tissue doppler of lateral left ventricular wall. At the end of the glycaemic monitoring were calculated for each patient the glycaemic variability and the incidence of hyperglycaemia and hypoglycaemia. Glycaemic variability refers to a blood glucose value of ≥ 200 mg / dL or ≤ 59 mg / dL detected more than 3 times in a day for at least 4 days. The inclusion criterion was the presence of diastolic heart
failure while the only exclusion criterion was the presence of diabetes diagnosis. Overall, 43 males and 57 females were enrolled with a mean age of 69.3 years (39-87 years) (Table 1). All patients underwent a timely glucose measurement at admission which excluded the presence of hyperglycaemia. No potentially hyperglycaemic drugs were added to the treatment during the hospital stay. Continuous glucose monitoring was performed as an integral part of the hospitalization diagnostic routine. In 94 of the 100 patients enrolled it was possible to conclude the analysis, detecting the glycaemic variability, the point glycaemia values and the estimated glycated haemoglobin value. A glycaemia ≥200 mg/dL was found in 53 patients (56%) while a high glycaemic variability was found in 51 patients (54%). A blood glucose value <59 mg/dl was found in 48 patients (51%). Only 5 times the estimated glycated Hb values were >7%. 32 of the patients who had at least 3 punctual glucose values ≥200 mg/dL were prescribed an oral glucose load curve, which in 100% of cases confirmed the diagnosis of diabetes (Table 2). No statistically significant differences were found based on age group or sex. In the control group, consisting of 10 patients without DHF undergoing continuous glucose monitoring at one of the participating cardiology units, an unknown hyperglycaemia was found in only 1 patient (10%) and a glycaemic variability in only 1 patient (10%) (Figure 1).

### Table 1: Anthropometric characteristics of sample

<table>
<thead>
<tr>
<th>Sample (No.)</th>
<th>100</th>
<th>Females</th>
<th>Males</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>39-87 yrs m 69.3±10.8</td>
<td>68.5±19.1</td>
<td>57.5±18.2</td>
<td>p=.000</td>
</tr>
<tr>
<td>Gender (No., %)</td>
<td>43%</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m2)(mean ± SD)</td>
<td>28.9±3.3</td>
<td>27.1±5.14</td>
<td>29.7±5.2</td>
<td>p=.000</td>
</tr>
<tr>
<td>Hypertension (No %)</td>
<td>Yes: 67%</td>
<td>Yes: 58%</td>
<td>Yes: 75%</td>
<td>p=.000</td>
</tr>
<tr>
<td>Hycolesterolemia (No %)</td>
<td>Yes: 55%</td>
<td>Yes: 58%</td>
<td>Yes: 49%</td>
<td>p=.000</td>
</tr>
</tbody>
</table>

![Patient 1: Hbc 6.0%, Glycemia 108 mg/dl](image1)

![Patient 2: Hbc 6.1%, Glycemia 110 mg/dl](image2)

**Figure 1:** Graphical reproduction of the glycaemic trend in two different patients with similar HBA1c and similar fast plasma glucose
5. Discussion

Glycemic Variability (GV) is a component of dysglycemia. Unlike glycated hemoglobin, it provides us with information on fluctuations in glucose levels. Thanks to the increase in the availability of Continuous Glucose Monitoring (CGM) devices, GV is the subject of growing interest from the scientific community and is becoming a new target for the treatment of diabetes. In the past, several studies have reported a positive association between GV and diabetic complications, both micro- and macrovascular [7, 8].

In recent years, new evidence suggests that GV is a predictor of all-cause mortality and Cardiovascular (CV) mortality, independent of HbA1c level [9-12]. It is likely that oscillating glucose is accompanied by an over-generation of free radicals, more than stable high glucose. Recent studies have confirmed, both in vitro and in vivo, the role of oxidative stress, produced during GV, in inducing endothelial dysfunction and inflammation, which leads with conviction to diabetic complications [13, 14]. The most relevant findings are the involvement of the AKT pathway in the process and the possibility that GV may induce higher DNA chromatin remodelling [15]. The increase in free radical production during the glucose fluctuation seems to be explained by an inefficient intracellular antioxidant response, due to a specific induction of microRNA-185 [16]. Increasing evidence indicates that high glucose fluctuations also increase oxidative stress in heart tissue and can induce cardiomyocyte apoptosis [17].

Diabetes is a major cause of HFpEF. However, it remains uncertain whether GV represents a new potential therapeutic strategy for preventing the development of HFpEF in patients with no known history of diabetes. VG could have important therapeutic implications. Recent evidence has shown the benefits of a category of drugs used for diabetes therapy (SGLT-2 inhibitors or GLP1 agonist receptor) in HFpEF patients with and without type 2 diabetes mellitus [18-22]. GCM might help identify the particular phenotype that best responds to treatment with SGLT-inhibitors.

Use of Glunovo amplify the possibility to investigate the glycemic variability and so can drive the medical therapy underline the necessity to treat with SLT-2 inhibitors or GLP1 agonist receptors.

6. Conclusions

Our experience suggests an incidence of hyperglycaemia and glycemic variability more than 65% in patients affected by HFpEF (Figure 2). If our data were reproducible on a large scale, a so high prevalence of diabetes in patients with HFpEF could explain the efficacy of SGLT-2 inhibitor and GLP-1 Agonist in this class of patients.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERGLYCEMIA</td>
<td>53(56%)</td>
</tr>
<tr>
<td>GLYCEMIC VARIABILITY</td>
<td>51(54%)</td>
</tr>
<tr>
<td>HYPOGLYCEMIA</td>
<td>48(51%)</td>
</tr>
<tr>
<td>Hb GLYCATED &gt; 7%</td>
<td>5(6%)</td>
</tr>
</tbody>
</table>

Table 2: Incidence of Glycemic alterations

Figure 2: Graphical reproduction of estimated incidence of diabetes based on our analysis
References


