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Original article

T2DM HEART FAILURE AND FIBROSIS MARKERS CORRELATION.

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Abstract

Background:

Despite many commonly used antihyperglycemic medications lowering hyperglycemia in type 2 diabetics, heart failure remains a major issue. Thus, variables other than glycemia may increase the risk of heart failure in diabetics.

Aim:

The primary aim of the current investigation was to assess the correlation between circulating biomarkers indicative of fibrosis and the occurrence of HFpEF in individuals diagnosed with T2DM, undergoing treatment with SGLT2i.

Methods:

Initially, the study conducted transthoracic echocardiography and laboratory analysis to measure various biomarkers. After a period of three years, data regarding heart failure events, including hospitalisations for heart failure and diagnoses of heart failure in outpatient settings by cardiologists, was collected.

Results:

Seventy-two patients were included in the study. The mean age was 57 (49.7; 63.2) years; 44% were female. Most patients had T2DM for more than 4 years. All patients were overweight or had obesity, and 93% patients had arterial hypertension (AH). After 3 years of follow-up, HFpEF was established in 21% patients. Patients were divided into two groups according to the presence of HFpEF, and baseline characteristics were compared. Patients with HF were older and had longer diabetes and AH duration and higher Nt-proBNP, Gal-3, PIIINP, and PICP levels at baseline than patients without HF (all p < 0:05).

Conclusion:

Patients with type 2 diabetes mellitus (T2DM) who were given sodium-glucose cotransporter 2 inhibitors (SLGT2i) and developed heart failure with preserved ejection fraction (HFpEF) after a three-year monitoring period had elevated serum concentrations of PICP, PIIINP, Gal-3, and NT-proBNP at the start of the study. Additionally, Gal-3 levels independently predicted HFpEF.

Recommendation:

SGLT2i are recommended in patients with T2DM at high risk of CV events or with CV disease to reduce hospitalizations for HF, major CV events, and CV death.

Keywords: Type 2 diabetes mellitus, type 1 diabetes mellitus, heart failure, fibrosis markers,
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1. Introduction.

Type 2 diabetes mellitus (T2DM) is a global epidemic that is anticipated to afflict approximately 592 million people by 2035, up from 382 million in 2013 and possibly underestimated [1, 2]. T2DM and type 1 diabetes mellitus have diverse clinical presentations and disease progressions [3]. This review will focus on T2DM pharmacological therapies and their effects on heart failure (HF) development because T2DM accounts for 90% to 95% of diabetic mellitus cases [4]. Diabetics are twice as likely to develop HF [5, 6].

The Framingham Heart Study found that diabetes mellitus alone raises the incidence of HF by 2-fold in men and 5-fold in women compared to age-matched controls, indicating an unknown sex disparity [7, 8]. Diabetics had a higher risk of HF even after controlling for age, hypertension, hypercholesterolemia, and coronary artery disease. Thus, diabetic cardiomyopathy was first used over 40 years ago to explain ventricular failure in diabetics without coronary artery disease or hypertension [9]. Its application has been expanded to define diabetes mellitus' higher myocardial dysfunction vulnerability.

Several studies have demonstrated that sodium glucose cotransporter 2 inhibitors (SGLT2i) have a notable impact on reducing the risk of heart failure in patients diagnosed with T2DM [7–9]. SGLT2i are recommended for patients diagnosed with type 2 diabetes mellitus (T2DM) who are at a heightened risk of cardiovascular (CV) events or have pre-existing CV disease. The administration of SGLT2i has been shown to effectively decrease hospitalisations related to heart failure (HF), major CV events, and CV-related mortality [9]. In addition to metabolic and hemodynamic protective mechanisms, SGLT2i demonstrate anti-inflammatory, antiapoptotic, and antifibrotic properties [10]. Moreover, extensive investigations conducted on both animal models and human subjects have consistently revealed a notable inhibitory impact on sympathetic nerve activation [10]. While the advantageous impacts of SGLT2i have been established, there exists a scarcity of data pertaining to prognostically significant biomarkers of fibrosis in individuals diagnosed with T2DM who have undergone treatment with SGLT2i. Hence, the primary aim of this research endeavour was to evaluate the correlation between circulating biomarkers associated with fibrosis and the occurrence of heart failure with preserved ejection fraction (HFpEF) in patients diagnosed with type 2 diabetes mellitus (T2DM) who were undergoing treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i).

2. Materials and Methods.

2.1. Study Design.

A prospective study was conducted within the population of patients diagnosed with Type 2 Diabetes Mellitus (T2DM). The investigation was carried out at a tertiary healthcare facility.

2.2. Data Collection.

Clinical, laboratory, and instrumental data were gathered during the initial assessment. Following a three-year period of post-treatment monitoring, pertinent data regarding heart failure (HF) incidents and other medically significant information were extracted from patients' medical records. Additionally, upon completion of the study, echocardiography, HbA1c levels, fasting lipids, and creatinine levels were assessed. Patient data including demographic characteristics such as age, gender, weight, height, body mass index (BMI), waist circumference (WC), medical background, and duration of diabetes were obtained from the patients' medical records. Abdominal obesity was operationally defined as a waist circumference exceeding 88 cm in females and surpassing 102 cm in males, according to established medical criteria. A baseline assessment was conducted, which involved acquiring a twelve-lead electrocardiogram (ECG) and a transthoracic echocardiogram. The cardiologist ruled out the presence of cardiovascular disease and heart failure. Echocardiography (VIVID 9 GE, USA) was conducted in accordance with the established

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standard protocol by a single operator. The left atrial volume (LAV) and left ventricular myocardial mass (LVMM) were adjusted for body surface area (BSA) and height using different allometric powers in accordance with medical and academic standards.

2.3. Statistical Analysis.

The data were analysed utilising the IBM SPSS statistical software (version 21.0, IBM Corp, USA). Continuous variables are typically represented using the median (interquartile range), while categorical variables are commonly expressed as the count (percentage). The statistical analysis employed to examine the disparities between groups involved the utilisation of the Mann–Whitney U test. Categorical variables were assessed using the chi-squared test for statistical comparison. A receiver operating characteristic (ROC) analysis was conducted to evaluate the performance of biomarkers. To elucidate the concept of relative risk, we computed the odds ratio (OR) along with its corresponding 95% confidence interval (95% CI). A logistic regression analysis was conducted to ascertain the potential risk factors associated with heart failure (HF). All pertinent demographic and clinical characteristics were thoroughly examined as potential prognostic factors. Firstly, the candidate variables were examined in univariate models. If the p-value was found to be less than 0.1, the corresponding variable was incorporated into a multivariable logistic regression model. Statistical significance was operationally defined as a p-value less than 0.05, indicating a level of significance commonly accepted in medical and academic research.

3. Results.

A total of seventy-two individuals were enrolled as participants in the current investigation. At the initial stage a number of 173 patients were examined for eligibility, however 101 patients were excluded from this study due to not being eligible.

All patients presented with T2DM and did not exhibit any cardiovascular events. The average age of the participants in the study was 57 years, with females accounting for 44.4% of the total population. The majority of patients exhibited a diagnosis of T2DM for a duration exceeding four years. All subjects exhibited a high BMI indicative of overweight or obesity, and a majority of 67 individuals (93%) presented with pharmacologically managed arterial hypertension. A total of forty-nine individuals (comprising 68% of the sample) were administered statins, resulting in a mean low-density lipoprotein (LDL) level of 2.68 millimoles per litre (mmol/L). The average glycated haemoglobin (HbA1c) level observed in the study population was 8.4%. It is important to note that all participants were administered oral antihyperglycemic medications as part of their treatment regimen. Empagliflozin at a dosage of 10 mg per day was prescribed for all patients in the study.

The study cohort was stratified into two distinct groups based on the presence of HFpEF. Baseline data were compared between the control group and the experimental group in order to establish a comparative analysis. The cohort of individuals diagnosed with HFpEF exhibited advanced age compared to the cohort without HFpEF. Additionally, the patients with HFpEF presented with a prolonged duration of both diabetes and arterial hypertension. There were no significant variations observed in terms of gender, smoking history, systolic and diastolic office blood pressure, body mass index (BMI), glycated haemoglobin (HbA1c), and glucose levels among the study participants.

The group diagnosed with HF exhibited significantly greater waist circumference measurements and a higher prevalence of abdominal obesity in comparison to the group without heart failure (non-HF group) (all $p < 0.05$). Patients diagnosed with HF exhibited significantly elevated levels of N-terminal pro-brain natriuretic peptide (Nt-proBNP) at the beginning of the study compared to patients without HF ($p = 0.001$). Patients diagnosed with heart failure (HF) exhibited significantly elevated levels of Galectin-3 (Gal-3) at the beginning of the study compared to patients without HF ($p = 0.012$). Similar findings were noted for PIIINP, as concen-

trations of this biomarker were found to be significantly elevated in the group with heart failure (p = 0.033). Patients diagnosed with HFpEF exhibited significantly elevated levels of procollagen type I carboxy-terminal propeptide (PICP) in comparison to patients without heart failure (nonHF). The median PICP levels were measured at 137 ng/ml (116.3; 175.5) for HFpEF patients and 115.2 ng/ml (71.8; 152.6) for nonHF patients, resulting in a statistically significant difference (p = 0.026).

There were no statistically significant differences observed in the baseline therapy for AH and T2DM, administration of statins, glomerular filtration rate (GFR) levels, and concentrations of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) between the two groups. Similarly, no significant differences were found in the baseline myocardial morphofunctional parameters (p > 0.05) between the groups. Simultaneously, there existed a disparity in the duration of therapy involving SGLT2i. Patients in the heart failure (HF) cohort exhibited a lower likelihood of receiving empagliflozin for a duration exceeding one year compared to patients in the non-heart failure (non-HF) cohort, with percentages of 40% and 71.9%, respectively (p = 0.01).

4. Discussion.

Twenty-one percent of participants in our research study exhibited HFpEF following a three-year period of observation. The individuals in question exhibited clinical risk factors, including age, abdominal obesity, duration of T2DM, and arterial hypertension, which have been linked to the occurrence of heart failure [10]. Obesity is a widely recognised risk factor for HF, and the presence of visceral adiposity may potentially contribute to the association between obesity and HF [11]. In our research, WC was identified as a notable indicator of abdominal obesity, exhibiting a statistically significant increase in patients who developed heart failure (HF). Indeed, it has been reported that among individuals diagnosed with T2DM, an excessive accumulation of visceral adipose tissue exhibits a more robust correlation with the onset of Left Ventricular Diastolic Dysfunction (LVDD) compared to glycemic control [12]. An elevation in the duration of T2DM is likewise correlated with an escalated susceptibility to heart failure (HF) [13]. Hence, our findings align with the data obtained from previous research, indicating that the continuous administration of SGLT2 inhibitors did not alter this correlation. While not all patients were administered SLGT2i for a duration of three years, it is noteworthy that the proportion of patients belonging to the HF group who received treatment for over a year was comparatively lower than that observed in the non-HF group. This discrepancy has the potential to influence the final outcome of the study.

Cardiac fibrosis has been extensively documented to be intricately linked with HF in medical literature. Due to the prevailing synthe- sis of type I and III collagen relative to their degradation, there is an accumulation of excessive collagen type I and III fibres within the myocardium [14]. There exists a diverse range of biomarkers that are indicative of various stages of therapeutic drug monitoring (TDM) pathogenesis and have the potential to forecast cardiovascular (CV) risk [6, 15]. In the current investigation, it was observed that patients who developed HFpEF within a span of three years exhibited increased levels of procollagen type I C-terminal propeptide (PICP), a biomarker associated with collagen type I synthesis, as well as procollagen type III N-terminal propeptide (PIIINP), a biomarker associated with collagen type III synthesis. Prior research has indicated that levels of serum PICP (procollagen type I C-terminal propeptide) are elevated in individuals with hypertension and exhibit a robust association with myocardial collagen composition [16]. Moreover, it has been observed that in individuals diagnosed with heart failure (HF) and preserved ejection fraction (EF), the concentrations of procollagen type I amino-terminal peptide and procollagen type III amino-terminal peptide in the plasma were found to be correlated with elevated rates of mortality and hospitalisation due to cardio-

vascular events [17]. Additionally, Procollagen Type III N-terminal Propeptide (PIIINP) and Collagen Type I Carboxy-terminal Telopeptide (ICTP), which are both collagen biomarkers, exhibited a correlation with the development of HFpEF, but not Heart Failure with Reduced Ejection Fraction (HFrEF) [18]. The intricate equilibrium between the biosynthesis and breakdown of two distinct forms of collagens plays a pivotal role in dictating the anatomical and physiological alterations within the myocardium of individuals with heart failure and compromised glycemic condition [4]. Based on our data analysis, it is suggested that Procollagen Type III N-Terminal Propeptide (PIIINP) could potentially serve as a predictive marker for HFpEF in patients with T2DM. Nevertheless, the complete comprehension regarding the potential of utilising these circulating indicators of collagen synthesis and degradation for prognosticating cardiovascular risk in individuals with metabolic disease remains uncertain [6]. Hence, further examination is warranted to determine the potential utility of PICP and PIIINP in enhancing prognostic outcomes in cardiac conditions linked to HF. This investigation should consider potential confounding factors that may influence collagen metabolism.

5. Conclusion.

Patients diagnosed with Type 2 Diabetes Mellitus and treated with Sodium-Glucose Cotransporter 2 inhibitors, who subsequently developed Heart Failure with preserved Ejection Fraction after a period of three years of observation, exhibited elevated levels of Procollagen Type I C-terminal Propeptide, Procollagen Type III N-terminal Propeptide, Galectin-3, and N-terminal pro-B-type Natriuretic Peptide in their serum samples at the beginning of the study. Furthermore, the concentration of Gal-3 was identified as an independent prognostic factor for the development of HFpEF. Further elucidation is warranted regarding the predictive value of certain biomarkers associated with fibrosis in individuals with T2DM within forthcoming investigations, while duly considering the pertinent economic considerations that underpin their utilisation. Conducting studies involving substantial sample sizes is imperative in order to ascertain individuals with T2DM who are at a heightened risk for the progression of HFpEF, by utilising personalised risk profiles for the purpose of targeted prevention and intervention strategies.

6. Limitations.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

7. Recommendation.

SGLT2i are recommended in patients with T2DM at high risk of CV events or with CV disease to reduce hospitalizations for HF, major CV events, and CV death.

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9. List of abbreviations.

T2DM- Type 2 diabetes mellitus
HFpEF- heart failure with preserved ejection fraction
SGLT2i- sodium-glucose cotransporter 2 inhibitors
AH- arterial hypertension
HF- Heart Failure
CV- Cardiovascular
BMI- Body mass index
WC- Wait circumference
ECG- electrocardiogram
LAV- left atrial volume
LVMM- left ventricular myocardial mass
BSA- body surface area

SPSS- Statistical Package for Social Sciences

ROC- receiver operating characteristic

OR- Odds ratio

CI- Confidence Interval

LDL- low-density lipoprotein

HbA1c- glycated haemoglobin

Nt-proBNP- N-terminal pro-brain natriuretic peptide

Gal-3- Galectin-3

PICP- procollagen type I carboxy-terminal propeptide

GFR- glomerular filtration rate

HDL- high-density lipoprotein

TG- triglycerides

LVDD- Left Ventricular Diastolic Dysfunction

TDM- therapeutic drug monitoring

PIIINP- procollagen type III N-terminal propeptide

EF- ejection fraction

ICTP- I Carboxy-terminal Telopeptide

HFrEF- Heart Failure with Reduced Ejection Fraction

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