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REVIEW ARTICLE

DIABETES MELLITUS WITH HEART FAILURE: BIOMARKERS FOR RISK ASSESSMENT AND PROGNOSIS

Ekta A. Andriyas[1], Abhishek Mishra[1], Neha Pant[1], Munzali Hamisu Umar[2], Arun Kumar Saxena[2], Imran Hussain[2]

1. Department of Medical Laboratory Technology, Era University, Lucknow.
2. Department of Medical Laboratory Sciences, Integral University, Lucknow.

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Abstract

As diabetes is becoming more commonplace globally, it is reasonable to anticipate a rise in the number of premature deaths linked to the disease and its consequences. It was estimated that diabetes directly contributed to five million fatalities in both developed and developing nations in 2017. In people with type 2 diabetes mellitus (T2DM), peripheral arterial disease, coronary heart disease, and heart failure (HF) were the most prevalent cardiovascular (CV) manifestations. In this regard, biomarkers representing different pathophysiological phases of type 2 diabetes may be highly promising in directing treatment. Furthermore, biomarkers provide significant diagnostic and prognostic information that cannot be obtained from objective data evaluation or clinical observation. In T2DM patients at higher risk of developing HF or who already have it, this review aims to provide an overview of the knowledge regarding the discriminative capacities of established new biomarkers.

Introduction:-

As diabetes is becoming more commonplace globally, it is reasonable to anticipate a rise in the number of premature deaths linked to the disease and its consequences. It was estimated that diabetes directly contributed to five million fatalities in both developed and developing nations in 2017 [1].In people with type 2 diabetes mellitus (T2DM), peripheral arterial disease, coronary heart disease, and heart failure (HF) were the most prevalent cardiovascular (CV) manifestations [2]. Compared to people without T2DM, patients with established diabetes have a twice higher prevalence of heart failure (HF) [3].The Reykjavík Study found that 0.4% of women and 0.5% of men had HF and T2DM overall [4].Therefore, the odds ratio (OR) for the relationship between poor glucose regulation and heart failure (HF) is 1.7 (95% CI = 1.4–2.1), and for the relationship between T2DM and HF is 2.8 (95% CI = 2.2–3.6) [5]. When compared to individuals without T2DM, people with T2DM had significantly worse short- and long-term prognoses, a probability of emergency hospitalization, and both fatal and non-fatal CV events [6]. When combined with classic CV risk factors, the development of T2DM is accompanied by several structural and functional alterations in the heart, arteries, skeletal muscles, adipose tissue, kidney, and other target organs [7, 8]. These changes raise the risk of heart failure. Clinical trials have demonstrated the beneficial effects of co-managing T2DM and HF on patients' prognosis and clinical trajectory [9-11]. In this regard, biomarkers representing different pathophysiological phases of type 2 diabetes may be highly promising in directing treatment. Furthermore, biomarkers provide significant diagnostic and prognostic information that cannot be obtained from objective data evaluation or clinical observation [12,13]. In T2DM patients at higher risk of developing HF or who already have it, this review aims to provide an overview of the knowledge regarding the discriminative capacities to establishe new biomarkers.

Corresponding Author:- Imran Hussain
Address:- Assistant Professor & Head, Department of Medical Laboratory Sciences Integral University, Lucknow.

Mechanism of HF Development due to Diabetes

The development of metabolic abnormalities in type 2 diabetes (T2DM) leads to cardiac dysfunction. These abnormalities are linked to increased fasting glucose, insulin resistance, lipotoxicity, and poor repair. Although the name diabetic cardiomyopathy is not commonly used, it describes the condition [14].In addition to non-traditional risk factors like ectopic calcification and osteoporosis, conventional CV risk factors like hypertension, dyslipidemia, abdominal obesity, asymptomatic atherosclerosis, CVD, and chronic kidney disease (CKD) can also contribute to the development of HF in diabetics [15].Therefore, oxidative stress with reduced nitric oxide bioavailability, fibrosis, local myocardial and microvascular inflammation, impaired cellular signaling (altered calcium homeostasis, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS)), endothelial dysfunction, and altered tissue reparation characterize cardiac dysfunction in T2DM patients. Additionally, secondary ischemic injury, cardiac myocyte apoptosis, and immunological alterations with subsequent subcellular component abnormalities (mitochondrial stress, endoplasmic reticular formation dysfunction, secretome shaping impairment) are also present [16].The hyperactivity of the sympatico-adrenal nervous system (SNS) and RAAS is directly linked to the development of heart dysfunction in type 2 diabetes (T2DM). Angiotensin-II, catecholamines, and aldosterone stimulate the production of advanced glycation end products (AGE) by acting as triggers of gluconeogenesis, lipolysis, and glycolysis. These AGEs, in conjunction with insulin and glucose, activate the transforming growth factor beta 1 (TGF1)/SMAD signaling pathways via the appropriate cell surface receptors (RAGE). Consequently, unfavorable cardiac remodeling, the acceleration of atherosclerosis, and deteriorating vascular integrity and endothelial function are correlated with increased oxidative stress, inflammatory response, and fibrotic extracellular matrix alteration with collagen cross-linking [17].

Diabetes Biomarkers in known HF cases

Biomarkers have been proposed as viable substitute indicators of pathologic alterations in target organs (skeletal muscles, kidney, arteries, and heart) and metabolic balance; they are especially thought to have diagnostic and prognostic value for individuals with T2DM and HF [18].Despite some differences in recommendations for practical use, current clinical guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and European Cardiology Society (ESC) have suggested the use of biomarkers in the personalized medical care of heart failure (HF) patients, regardless of type 2 diabetes (T2DM), to diagnose HF and stratify patients at higher risk of poor prognosis [19].The ACC/AHA/HFSA HF guidelines include novel biomarkers of fibrosis and inflammation (soluble suppression of tumorigenicity-2 (sST2) and galectin-3 (Gal-3) as an alternative tool for CVD prediction and HF risk stratification, but their clinical utility is questionable has not yet been demonstrated in T2DM [20].

Biomarkers

Natriuretic Peptides

Myocardial strain, volume overload, inflammation, and ischemia/hypoxic damage cause the release of natriuretic peptides (NPs) from cardiac myocytes. NPs, which function as physiological antagonists of RAAS, prevent cardiovascular remodeling by suppressing apoptosis, inflammation, and fibrosis, attenuating water and sodium homeostasis, potentiating vasodilation and vascular reparation, and reducing insulin resistance in the heart and skeletal muscles. Furthermore, there is compelling evidence for the protective ability of NPs in tissue, which has improved clinical outcomes and lowered the risk of HF readmission [21, 22].A significant rise in NP serum levels is linked to the development of heart failure (HF) and is intimately linked to the risk of CV death and HF hospitalization [58]. However, reducing NP serum levels was closely linked to improvements in clinical outcomes and prognoses in individuals with HFrEF and HFpEF. Naturally occurring proteins (NPs) have been used as a diagnostic and prognostic tool for biomechanical stress, primarily for heart failure (HF) with reduced ejection fraction (HFrEF) [23].

Cardiac Troponins

Elevated levels of hs-cTn were found to be indicative of subclinical myocardial injury, which developed separately with the progression of both T2DM and HF. The membranes of cardiac myocytes can be harmed by metabolic and oxidative stress, which can also cause cytoplasmic troponin to leak through. Furthermore, structuring the complex with AGE has demonstrated the emergence of irreversible cardiac troponin changes [24].Regardless of the presence of T2DM, circulating levels of hs-cTn provide important predictive information for patients with HFpEF and HFrEF, despite the fact that these patients have significantly higher levels of hs-cTn than those without T2DM. Moreover, hs-cTn can distinguish T2DM individuals with an exceptionally high absolute risk of CVD since it predicts unfavourable outcomes separately from NT-proBNP [25].Willeit P. et al. (2017) revealed that individuals in the general population with high hs-cTn concentrations within the normal range were linked to an elevated risk of

CVD in a meta-analysis of 28 pertinent studies. According to the ARIC (Atherosclerosis Risk in Communities) study, higher incident CHD (hazard ratio [HR] = 2.20; 95% CI, 1.64–2.95), ischemic stroke (HR = 2.99; 95% CI, 2.01–4.46), atherosclerotic CVD (HR = 2.36; 95% CI, 1.86–3.00), HF hospitalisation (HR, 4.20; 95% CI, 3.28–5.37), and all-cause mortality (HR, 1.83; 95% CI, 1.56–2.14) are all associated with elevated hs-TnI (3.8 ng/L) in the general population [26].

Adrenomedullin

Adrenomedullin's C-terminal inactive component, known as mid-regional pro-atrial natriuretic peptide (MR-proADM), mediates both natriuretic and vasodilatory effects.
It has been discovered to have potential diagnostic and prognostic utility, being high in acute HF and severe chronic HF, especially in HFrEF, albeit the results of clinical trials were controversial [27]. In terms of predicting short-term mortality, the BACH (Biomarkers in Acute Heart Failure) experiment has demonstrated that MR-proADM is more accurate than both BNP and NT-proBNP. In patients with overt HF, serum levels of mid-regional pro-adrenomedullin (MR-proADM) were linked to all-cause mortality and 1-year CV events[84]. Nonetheless, Vazquez-Montes MDLA et al. (2020) found that in the prediction of chronic heart failure, MR-proADM was not more accurate than NT-proBNP. Huang Z. et al. (2020) conducted a meta-analysis that was just published, assessing the diagnostic usefulness of new biomarkers for heart failure [28].

Soluble Suppression of Tumorigenicity-2

One well-established biomarker of inflammation and fibrosis is soluble suppression of tumorigenicity-2 (sST2), which has some predictive power. By interfering with interleukin-33, ST2 causes the transmembrane isoform ST2 ligand to be expressed more frequently on the surfaces of target cells, which in turn causes biomechanical myocardial stress, damage, and inflammation. Ultimately, by reducing hypertrophy and inhibiting fibrosis, sST2 improves survival by protecting the myocardium [29].The experts from the ACC/AHA/HFSA have approved sST2 as one of the inflammatory biomarkers for use in risk stratification of patients with HF because it has shown high accuracy and repeatability in serial measurements at a reasonable cost and because it adds predictive value to cardiac troponins and NPs for HF. Furthermore, independent of common CV, sST2 exhibits a significant discriminative ability in predicting hospitalisation and morbidity from CV events, as well as metabolic comorbidities such hypertension, renal dysfunction, and diabetic kidney disease. Additionally, sST2 can categorise patients with HFrEF who are more likely to die suddenly. Additionally, elevated levels of sST2 outperform NT-proBNP in providing extra prognostic information for certain HF phenotypes [30-33]. Therefore, regardless of the presence of T2DM, sST2 appears to be a strong predictor of clinical outcomes in HF patients. However, the primary barrier to the routine use of single and serial sST2 assessments in clinical practice is thought to be the high cost.

Galectin-3

Galectin-3 is a member of the galectin family and binds to galactosidase [34].It regulates cell development, proliferation, differentiation, apoptosis suppression, pre-mRNA splicing, angiogenesis attenuation, inflammation reduction, and fibrosis, among other biological processes. It has been demonstrated that whereas over-expression of galectin-3 was linked to tissue protection, a deficit in the protein causes tissue harm. Furthermore, galectin-3 has potential therapeutic efficacy and functions as a predictive cardiac biomarker [35,36].Levels of galectin-3 were linked to fat compartments, incidence T2DM, and T2DM prevalence, according to the Dallas Heart Study. Furthermore, hs-CRP, IL-18, monocyte chemoattractant protein 1, soluble TNF receptor 1A, myeloperoxidase, C-peptide, and the homeostatic model assessment for insulin resistance were all favourably linked with galectin-3 levels. Furthermore, elevated risk of all-cause death, CVD, and progressive renal disease in type 2 diabetes are all independently correlated with serum galectin-3 [37,38].It has been demonstrated that HF patients had higher serum levels of galectin-3, which has been linked to CAD, unfavourable cardiac remodelling, atrial fibrillation, and myocardial fibrosis. Moreover, galectin-3 is thought to be a modulator of the advancement of type 2 diabetes in addition to being a potent predictive biomarker of incident HF. Galectin-3 levels in HFpEF patients were inversely correlated with LV ejection fraction and were positively correlated with age, creatinine clearance, arterial stiffness (measured by carotid femoral pulse wave velocity), aldosterone, and BNP levels [39,40].

Conclusion:-

We discovered that in patients with HFpEF, significant heterogeneity in CV risk variables, such as T2DM, hypertension, and atherosclerotic CVD, makes it more difficult to stratify and forecast risk accurately. New biomarker-based methods would therefore be sufficient to enhance risk stratification and the prognostication of

unfavorable clinical outcomes. A diagnosis of HFpEF is not ruled out in patients with diabetes, even though current risk stratification procedures for HFrEF patients are focused on the measurement of NP levels. Multiple biomarkers, including NPs, sST2, and cardiac troponins, were found to be highly predictive of hospitalization and all-cause death in HFrEF; however, in symptomatic HFpEF, this combined model may have prognostic significance. Their significance in T2DM patients with asymptomatic HFpEF and diastolic dysfunction is still unknown, nevertheless.The prognosis of T2DM patients with concomitant HFpEF can be determined using novel biomarkers of inflammation (mid-regional pro adrenomedullin), fibrosis (galectin-3), and collagen turnover biomarkers, regardless of NPs. However, large clinical trials are needed to clarify the role of these biomarkers in point-of-care and routine clinical practice. For the individualized, biomarker-oriented treatment of T2DM patients at high risk of HF and overt HF, several biomarker models seem to be feasible. Still, the primary obstacle is the high expense of biomarker-guided administration for putting this strategy into regular clinical practice.

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