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Association between Elevated N-Terminal Pro-Brain Natriuretic Peptide and Cardiovascular Complication among Type-2 Diabetic Patients in Gaza Strip

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Abstract

The number of patients with type -2 diabetes (T2DM) with cardiovascular complication is progressively increasing all over the world. The burden of T2DM with cardiovascular complication is now a huge Palestinian public health challenge increase substantially in the last two decades. The natriuretic peptide is important in controlling blood pressure and saltwater balance. B-Type Natriuretic Peptide (BNP) and N-Terminal pro-B-Type Natriuretic Peptide (NT-proBNP) are small peptides that are either hormones or part of the peptide that contained the hormone at one time. They are continually produced in small quantities in the heart and released in larger quantities when the heart senses that it needs to work harder. The aim of the study was to investigate association between elevated N-terminal pro-brain natriuretic peptide and cardiovascular complication among Type-2 diabetic patients in Gaza strip.

Method: The study design was case-control consist of 180 participants aged 45 to 65 years divided into three groups. The first group is 60 healthy participants as control (group 1) attending Al-Remal central clinic, Gaza. The second group was 60 participants with T2DM without CVD (group 2) who also attending at Al- Remal central clinic and last group were T2DM with the cardiovascular complication at the Cardio Care Unit (CCU) at El-Shifa hospital (group 3). Three groups were matched for age and the period of study was from June to October 2018. All subjects were investigated for biochemical markers, serum NT-BNP were determined By ELISA techniques.

Results: The results pointed out that there was a significant difference between three studied groups in the gender, BMI, smoking, and level of hypertension ($P<0.05$). Also, the results illustrated that patients T2DM with CVD complication were higher statistically significant of duration and age at onset than T2DM without CVD patients. The results of the study showed that the average of NT-BNP level was higher statistically significant in T2DM with CVD compared without CVD and controls. In contrast, no statistically significant for NT-BNP level T2DM with CVD and without CVD. By same away, the mean of cardiac enzymes (LDH, CK & CKMB) were higher statistically significant in T2DM with CVD compared with T2DM without CVD and controls ($P<0.001$). However, the results showed that there is a positive significant correlation between NT-BNP and BMI, Blood pressure (Systolic and Diastolic), CKMB and LDH ($P<0.05$).

Conclusion: Results of this study recommended that serum NT-BNP not utility as a cardiac biomarker in CVDs predication in T2DM patients. And there are positive association between NT-BNP and BMI, Blood pressure (Systolic and Diastolic), CKMB and LDH.

Keywords: NT-BNP; T2DM; Cardiovascular disease; Cardiac enzymes; Gaza strip

Introduction

The prevalence of T2DM gradually increases in the world especially with present a family history [1]. Screening for renal and eyes complications is already a recognized part of routine T2DM health care today, but there is no similar reoccurring screening for CVD of diabetes [2,3]. This may be due to not available of cost-effective methods and time consuming for an echocardiographical examination. The most evident cardiac complication among T2DM is coronary atherosclerosis, Acute Myocardial Infarction (AMI), ischemic heart disease and atherosclerosis [4]. T2DM is also more incidences among patients with heart disease [5]. In several studies, Gender is the risk to develop heart failure (male>female) among T2DM [6]. Moreover, patients with T2DM have an irregular elevated in left ventricular mass independent of blood pressure [7]. Additionally, several factors may contribute to increased myocardial stiffness. A meta-analysis showed that left ventricular hypertrophy has been

associated with 3 fold increased risk of future CVD morbidity and 4 fold increase of all-cause mortality [8,9]. Thus, taken together, there are several mechanisms besides the more aggressive atherosclerosis that could explain why diabetes patients with cardiovascular complications have higher morbidity and mortality.

B-type Natriuretic Peptide (BNP) is 32-amino acid peptide an are small peptide synthesized in the left ventricle of the heart as the 108-amino acid prohormonepreproBNP (γ-BNP) [10] and BNP is produced by cleaving the signal peptide then two proprotein convertase, Corin and Furin cleave γ-BNP to form a biologically active hormone to produced NH2-Terminal Portion proBNP (NT-proBNP) and free BNP. Increased secretion of BNP and Nt-proBNP occurs mainly with elevated tension in the ventricular walls, decreased oxygen supply, AMI, chronic cardiac heart failure, and in hypertrophy of the heart [11]. However, several studies pointed out that there is NT-proBNP is play vital role in predication CVD among T2DM [12-15]. The aim of the study was investigated N-terminal pro-brain natriuretic peptide status and some biochemical parameters among Type-2 diabetic with cardiovascular disease in Gaza.

Material and Methods

Case-Control Study Design: This study was conducted in the laboratory of Central laboratory in Remal Clinic, Gaza Strip-Palestine in the period from March to October 2018. The study included 180 subjects divided to the three groups: 60 as control, 60 T2DM patients and 60 T2DM with CVD, matching for age between three studied groups aged 45 to 65. Vacutainer serum and EDTA blood samples were collected from all participants for the laboratory analysis. This study was conducted in Gaza strip- Palestine at the Central laboratory of Al-Remal clinic during the period from June to October2018.

Study population

The study population was comprised patients with diabetic patients type-2 without CVD complication recruited from the outpatient clinic at the Diabetic Department of Remal Clinic Center in Gaza Strip and type 2 diabetic patients with CVD complication recruited from the Cardio Care Unit (CCU) at El- Shifa Hospital, Gaza Control group was an equal number of an age-matched.

Ethical considerations

Permission study was obtained from the Helsinki committee in the Gaza Strip and admin approval was obtained from the human resource development general directorate in the Ministry of Health. Moreover, consent informed were gained from all participants before enrolment in the study after explained study's objectives and anonymity, right and confidentially were saved.

Inclusion criteria

All of the diabetic type-2 patients with or without CVD were included in the study.

Exclusion criteria

Patients with liver diseases, Type 1 diabetic patients and Patients with kidney failure.

Sample size and collection

In this study 180 subjects, their age ranged from (45-65) years, were selected and divided into three groups: group 1 include 60 healthy subjects served as control, group 2 comprise 60 patients type 2 diabetics without cardiovascular disease who underwent routine medical checkups at El-Shifa Hospital and had no medical history of CVDs and group 3 included 60 subjects type 2 diabetic with cardiovascular disease who were referred to the cardio care unit of the Cardiology Department, El-Shifa Hospital, Gaza strip, Palestine and recruited from the Cardio Care Unit at El-Shifa (CCU) at El-Shifa Hospital, Gaza. A meeting interview was used for filling in a questionnaire which designated for matching the study need. All interviews were conducted face to face by the researcher herself. The questionnaire included questions on demographic and clinical data. Venous blood samples were collected (about 5 ml) was drawn into serum vacationer tubes for LDH, CK, and CKMB by chemistry autoanalyzer (Erba XL 200) and NT-BNP by Eliza kit (R&D company). These biochemical tests are done in the laboratory in Remal clinic. 120 T2DM patients with CVDs.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Science (SPSS) version (22) soft-ware the USA for windows. Descriptive statistics will be reported as Mean ± SD and ANOVA test P values ($P<0.05$) will be considered statistically significant. Sample distribution of the study variables and the cross-tabulation were applied. Descriptive was described by mean ± Standard Deviation (SD) and range as a minimum and maximum values were used.

Results

Descriptive variables in the three studied groups

Table 1 summarize general demographic variables, that the three studied groups were contains 35 (58.3 %) males and 25 (41.4 %) females in control, group1, in T2DM without CVDs group 2 were contain 38 (63.3%) males and 22 (36.7%), while T2DM with CVDs group 3 contain 23 (38.3%) male and 37 (61.7%). The means age for the three were 53.8 ± 6.5, 53.9 ± 5.6 and 55.6 ± 6.9. There was no significant difference according to age because the study groups were matched for age. Regard to BMI the mean were 26.9 ± 3.2, 32.2 ± 6.6 and 32.4 ± 6.9 kg/m^2 for control, T2DM without CVDs and T2DM with CVDs respectively. ANOVA test clarified that there was a significant difference ($p<0.001$) in the studied group according to BMI. However, Post hoc elucidated that there was a significant difference between group 2 and group 3 ($p<0.001$) compared with group 1 while there are no significant difference between group 2 and group 3. Add to in smoking variable most participants are non-smoker category but it found 3.3 %, 11.7 % and 28.3% of participants in the three studied groups respectively are current smokers and ANOVA test defined that there was significant difference among studied groups ($p<0.001$) and post hoc has been appointed that there was a significant difference between group 2 and group 3 ($p <0.001$) in comparison with group 3 and no significant difference between group 2 and group 3. On the light of the present results, no significant difference was found among gender and age, add to smoking variable most participants are non-smoker category but it found small proportion of participants in the three studied groups respectively are current smoker and ANOVA test defined that there was significant difference among studied groups ($p<0.001$) and post hoc has been appointed that there was a significant difference between group 2 and group 3 ($p <0.001$) and no significant difference between group 2 and group 3., these results of BMI and smoking among studied groups. Conversely other studies found study show significant difference between BMI and smoking whereas similar to present study results unless. The reason for these conflicting results may be due to the variation in the sample size from study to others. As for the mean levels of systolic/diastolic blood pressure were 114.8 ± 5.7/128.8 ±15.7, 126.3 ± 8.7 and 74.3 ±6.1/84.3 ±11.4/ 81.7 ± 6.2 for group 1, group 2 and group 3 respectively. ANOVA test clarified

that there was a significant difference between three studied groups (p <0.001); post hoc explained that there was a significant difference in group 2 and group 3 in compared with group1, while there was no significant difference between group 2 and group 3 in systolic/diastolic blood pressure.

Duration and age at onset of diabetes in the Patients groups

Table 2 shows the mean values of diabetes duration and age at onset of DM between T2DM without CVDs and T2DM with CVDs. The mean values of diabetic duration and age onset of DM were 6.7 ± 4.9 years and 11 ± 9.2 years; 47.9 ± 7.1 years and 49.7 ± 9.5 years in the group 2 and 3, respectively. While the mean age at onset of DM was 47.9 ± 7.1 and 49.7 ± 9.5 for group 2 and 3, but regarding the mean age of onset, CVDs was 53.5 ± 5.9.

Results of the study clarified that there was a significant relationship between diabetes duration and CVD complication in T2DM patients. There was an increasing trend in the duration of diabetes, such increase was statistically significant (p<0.001) and this indicate that duration of DM was a risk factor for CVDs complication development in T2DM patients.

Cardiac biomarkers levels among the studied groups

Table 3 shows serum cardiac enzyme activities in the three studied groups including Lactate Dehydrogenase (LDH), Creatine Kinase (CK) and Creatine Kinase Muscle Brain (CKMB). The mean of LDH were 328.8 (210476), 363.5 ± 69.6 (240-592) and 467.4 ± 212.6 (261-1146) U/L among group 1, group 2 and group 3, respectively. ANOVA test showed a significant difference in the level of serum LDH among three groups (P<0.001), Post- hoc test revealed a significant difference between group 2 within group 3 and group 1 within group 3 (P<0.001). In contrast, no significant differences were found between group 1 and group 2.

However, on the other hand, the mean of CK and CKMB was gradually increased with values of 101.5 ± 39 (36-175), 124 ± 63.6 (47-290) and 208.8 ± 312.5 (57-1695) U/L for CK and 13.1 ± 4.3 (47-290), 20.8 ± 10.2 (9-61) and 34.4 ± 50.4 (10-280) for CKMB among Gr1, Gr 2 and Gr 3, respectively. The ANOVA test showed a significant difference in the mean level of serum CK among three groups (P <0.001) and Post-hoc test showed a significant difference between group 1 and group 3 (P<0.001), group 1 and 3.

Obviously, cardiac enzyme activities increase gradually among group 1, group 2 and group 3, respectively. This increase was clinical and statistically significant for group 3 compared with group 1 and group 2.cardiac enzyme activities increase gradually among three studied groups respectively. This increase was clinical and statistically significant for group three compare with group 2 and group 1. ANOVA test showed a significant difference in the level of serum LDH among three groups (P<0.001), Post- hoc test revealed a significant difference between group 2 and 3, group 1 and 3 (P<0.001). In contrast, no significant differences were found between group 1 and group 2. Also, ANOVA test showed a significant difference in the mean level of serum CK and CKMB among three groups (P<0.001) and Post-hoc test showed a significant difference between group one with group two and three (P <0.001).

Table 3 also showed serum NT-BNP mean 72.9 ± 45.2, 334.3 ± 121.8 and 306.2 ± 100.6 pg/ml among group 1, group 2 and group 3, respectively. ANOVA test showed a significant difference in the level of serum NT-BNP among three groups (p<0.001). Post-hoc test was clarified a significant difference between group 1 with group 2 and group 3 (p<0.001). In contrast, the results showed that there was no significant difference was found between group 2 and group 3. This indicated that NT-BNP predicts biomarkers for heart disease in T2DM patients.

Table 1: Demographic variables in the three studied groups.

Variables	Group 1 (Control)	Group 2 (T2DM)	Group 3 (T2DM &CVD)	χ^2	F	p-value
Gender N (%) Male N (%) Female N (%)	35 (58.3) 25 (41.7)	38 (63.3)[b] 22 (36.7)	23 (38.3) 37 (61.7)	4.352		0.014*
Smoking N (%) Non-smoker Past-smoker Current-smoker	55 (91.7) 3 (5) 2 (3.3)	34 (56.7)[a] 19 (31.7) 7 (11.7)	(56.7)[b] 9 (15) 17 (28.3)	11.955		<0.001*
Age by years Mean ± SD (Min-Max)	53.8 ± 6.5 (4565)	53.9 ± 5.6 (4565)	55.6 ± 6.9 (4565)		1.638	0.197
BMI (kg/m²) Mean ± SD (Min-Max)	26.9 ± 3.2[ab] (2233.4)	32.2 ± 6.6 (19-44.9)	32.4 ± 6.9 (2357.8)		17.559	<0.001*
Systolic blood pressure (mmHg) Mean ± SD (Min-Max)	114.8 ± 5.7 (100120)	128.8 ± 15.7 (105180)	126.3 ± 8.7 (100150)		27.999	<0.001*
Diastolic blood pressure (mmHg) Mean ± SD (Min-Max)	74.3 ± 6.1[ab] (6080)	84.3 ± 11.4 (65130)	81.7 ± 6.2 (7095)		23.232	<0.001*

(* [a,b,c]: significant atp ≤ 0.05),[a] compare for Group 1 *versus* Group 2; [b] compare Group 1 *versus* Group 3; [c] compare Group 2 *versus* Group 3); *p- value significant at p ≤ 0.05.

Table 2: Duration of diabetes in patient groups.

Variables	Group 2 (T2DM) Mean ± SD	Group3 (T2DM&CVD) Mean ± SD	t	p-value
Diabetic duration (years) Range	6.7 ± 4.9[c] 1-24	11 ± 9.2 1-40	-3.193	.000
Age at onset of DM (years) Range	47.9 ± 7.1[c] 24-61	49.7 ± 9.5 22-64	-1.176	.040
Age at onset of CVDs (years) Range	-	53.5 ± 5.9 39-63	-	-

(*,a ,b, c: significant atp ≤ 0.05, [a] compare for Group 1 *versus* Group 2; [b] compare Group 1 *versus* Group 3; [c] compare Group 2 *versus* Group 3); p-value significant at p ≤ 0.05.

Table 3: Cardiac biomarkers levels among the studied groups.

Biomarkers	Group 1 (Control)	Group 2 (T2DM)	Group 3 (T2DM &CVD)	p-value
NT-BNP (pg/ml) Mean ± SD (Min-Max)	72.9 ± 45.2[a b] 21.7-181.9	334.3 ± 121.8 73.6-593.1	306.2 ± 100.6 138.2-553.5	.000**
LDH Mean ± SD (Min-Max)	328.8 ± 62.4[b] 210-476	363.5 ± 69.6[c] 240-592	467.4 ± 212.6 261-1146	000
CK Mean ± SD (Min-Max)	101.5 ± 39[a b] 36-175	124 ± 63.6 47-290	208.8 ± 312.5 57-1695	.000
CKMB Mean ± SD (Min-Max)	13.1 ± 4.3[a b] 4-20	20.8 ± 10.2 9-61	34.4 ± 50.4 10-280	.000

(*, [a ,b, c]: significant atp≤0.05),[a] compare for Group 1 *versus* Group 2;; [b] compare Group 1 *versus* Group 3; [c] compare Group 2 *versus* Group 3).

Correlation between serum BNP level and other parameters in the studied groups

Correlation between serum BNP level and other parameters in the studied groups pointed out in table 4. The results showed that there is a positive significant correlation between NT-BNP and BMI, Blood pressure (Systolic and Diastolic), CKMB and LDH (P<0.05). In contrast, the results showed that no significant correlation between NT-BNP and age, T2DM duration and CK as total (P>0.05).

Discussion

Diabetic vascular complications represent the leading cause of morbidity and mortality in affected patients [16]. Heart diseases were the common causes of death among poor glycemic controls T2DM patient in Palestinians [17,18]. The results showed that there is an association between age and occurrence of cardiovascular complication among T2DM and duration of T2DM between in the Patients groups. O'Keefe JH, et al. and Wannamethee SG, et al. were illustrated that both early and late-onset of diabetes are associated with increased risk of major coronary heart disease events and mortality, but only early onset of diabetes appears to be a CHD equivalent [19,20]. This result was compatible with the study that showed an association between age at onset of DM and CVD development. Based on our result, there was a positive relationship between diabetes duration and CVD complication in T2DM patients and this agrees with other study showed that duration of DM had increases the risk of CHD death independent of coexisting risk factors [21-23]. Furthermore, Gimeno Orna JA, et al. demonstrated diabetes duration superior to 15 years significantly increased cardiovascular risk of the patients and they concluded that it could be useful to consider diabetes duration in order to stratify cardiovascular risk of type 2 diabetic patients [24].

The present study showed that the increase in serum LDH, CK and CKMB activities in the T2DM with CVDs group was significant compared to the T2DM without CVDs and control groups. Similar results were previously reported [25,26]. The significant elevation of LDH, CK and CKMB in T2DM with CVD may be explained by their specificity to CVDs diagnostic and our founding agree with others studies that illustrated cardiac enzymes have been demonstrated to be important prognostic determinants to identify high-risk patients [23, 27-30].

The results show that there is an association between T2DM and elevated NT-BNP. So this indicates NT-BNP is good to predict biomarkers for heart disease in T2DM patients. These results agreed with Santaguida PL, et al. found that NT-BNP as independent predictors of mortality, morbidity, or combined mortality and morbidity outcomes in persons with acute decompensated heart failure and Wang et al. provide additional prognostic information to NT-proBNP in the population the peptides are regarded as equal for the diagnosis of both acute and chronic heart failure [31,32]. By the same away Peleg A, et al. clarified that NT-BNP secretion depends on myocardial wall stress, hence the role of blood BNP as a marker of heart failure and they NT-BNP level may predict the outcome of acute coronary syndrome *via* a heart failure mechanism [33]. In contrast, Mitchell A, et al. found there was associated with NT-BNP level in this cross-sectional study of asymptomatic adults free of overt coronary artery disease, suggesting that higher NT-proBNP levels may reflect subclinical myocardial microvascular dysfunction [34].

Also, the results of the study coincide with Görmüs U, et al. that found NT-BNP levels known to be elevated in T2DM patients with asymptomatic diastolic dysfunction [35].

These findings have important clinical implications because patients with T2DM have an increased risk of developing CVDs. Identifying novel risk factors for CVDs may help in the development of strategies for the prevention and treatment of CVDs in T2DM patients. The mechanisms through which the NT-BNP levels and CVDs are associated were not clear. Studies have shown that the natriuretic peptide family may have a role as anti-migration factors for vascular smooth muscle cells [36]. They also have beneficial effects in T2DM with CVDs because natriuretic peptides can promote angiogenesis, modify the function of vascular endothelial cells, reduce cardiac load, and improve blood supply to the legs owing to their diuretic and vasodilator effects and BNP has a protective role in vascular disease [37-39]. Our data support the notion that higher BNP levels indicate to CVD complications development among T2DM patients.

However, because of the impairment of BNP receptors in atherosclerosis or ischemic vascular disease and the protective effect of BNP is weakened and BNP levels are increased in response to the severity of ischemia as a protective effect [40,41]. Nevertheless, the production and secretion of BNP is the result of a complex integration among mechanical, chemical, hemodynamic, humoral, ischemic, and inflammatory inputs in CVD, and the specific mechanism remains to be elucidated [42]. BNP is likely to be a new therapeutic strategy for

Table 4: Correlation between serum BNP level and other parameters in the studied groups.

Variables	NT-BNP (pg/ml)	
	r	P-value
Age (years)	0.078	0.298
BMI	0.316	0.000*
Systolic Blood pressure	0.374	0.000*
Diastolic Blood pressure	0.353	0.000*
T2DM duration (years)	0.039	0.676
CK (U/L)	0.091	0.225
CKMB (U/L)	0.217	0.003*
LDH(U/L)	0.165	0.027*

The correlation was analyzed using Pearson correlation coefficient. * p-value significant at $p \leq 0.05$.

T2DM patients with CVD. Higher BNP levels are associated with a higher prevalence of CVD in T2DM patients. Routine measurement of BNP levels can improve the predictive ability of CVD in T2DM patients.

Conclusion

Our study supplies a preliminary elucidation of the clinical value of the NT-BNP levels in the risk assessment of CVDs in T2DM patients. Our findings show that routine measurement of NT-BNP levels can mot improves the predictive ability of CVDs in T2DM patients. Our findings are expected to encourage designing future studies with larger cohorts of patients from different ethnic populations. Further studies are warranted to determine if plasma NT-BNP levels are changed in patients with cardiovascular complications over a longer period following medical treatment and if the changes correlate with the underlying pathology. Such studies shall help to understand the diagnostic and prognostic values of furin and may also help to translate basic discoveries in furin research into novel strategies to treat cardiovascular complications.

Declaration of Interest

The authors report no declarations of interest.

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References

1. Papazafiropoulou AK, Papanas N, Melidonis A, Maltezos E (2017) Family History of Type 2 Diabetes: Does Having a Diabetic parent Increase the Risk? Curr Diabetes Rev 13: 19-25.
2. Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, et al. (2017) Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 5: 431-437.
3. Radwan M, Elsous A, Al-Sharif H, Abu Mustafa A (2018) Glycemic control among primary care patients with type 2 diabetes mellitus in the Gaza Strip, Palestine. Ther Adv Endocrinol Metab 9: 3-14.
4. Prasad K (2012) Resveratrol, Wine, and Atherosclerosis. Int J Angiol 21: 7-18.
5. Braunwald E (2019) Diabetes, heart failure, and renal dysfunction: The vicious circles. Progress in Cardiovascular Diseases.
6. Leiter LA, Bain SC, Hramiak I, Jódar E, Madsbad S, et al. (2019) Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. Cardiovasc Diabetol 18: 73.
7. Levelt E, Mahmod M, Piechnik SK, Ariga R, Francis JM, et al. (2016) Relationship Between Left Ventricular Structural and Metabolic Remodeling in Type 2 Diabetes. Diabetes 65: 44-52.
8. Huxley RR, Filion KB, Konety S, Alonso A (2011) Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 108: 56-62.
9. Elsous A, Radwan M, Al-Sharif H, Abu Mustafa A (2017) Medications Adherence and Associated Factors among Patients with Type 2 Diabetes Mellitus in the Gaza Strip, Palestine. Front Endocrinol 8: 100.
10. Tateyama H, Hino J, Minamino N, Kangawa K, Ogihara T, et al. (1990) Characterization of immunoreactive brain natriuretic peptide in human cardiac atrium. Biochem Biophys Res Commun 166: 1080-1087.
11. Semenov AG, Tamm NN, Seferian KR, Postnikov AB, Karpova NS, et al. (2010) Processing of pro-B-type natriuretic peptide: furin and corin as candidate convertase. Clin Chem 56: 1166-1176.
12. Looker HC, Colombo M, Agakov F, Zeller T, Groop L, et al. (2015) Protein biomarkers for the prediction of cardiovascular disease in type 2 diabetes. Diabetologia 58: 1363-1371.
13. Son JW, Kim S (2015) Dipeptidyl Peptidase 4 Inhibitors and the Risk of Cardiovascular Disease in Patients with Type 2 Diabetes: A Tale of Three Studies. Diabetes Metab J 39: 373-383.
14. Gupta V, Teli V (2019) 2210-PUB: Despite Optimal Use of Angiotensin Receptor Blockers There Exists Substantial Cardiovascular Risk as Suggested by Elevated NT-ProBNP in 259 T2DM Patients. Am Diabetes Assoc 68.
15. Colombo M, Looker HC, Farran B, Agakov F, Brosnan MJ, et al. (2018) Apolipoprotein CIII and N-terminal prohormone b-type natriuretic peptide as independent predictors for cardiovascular disease in type 2 diabetes. Atherosclerosis 274: 182-190.
16. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, et al. (2017) Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors *versus* other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol 5: 709-717.
17. Ei Bilbeisi AH, Hosseini S, Djafarian K (2017) The Association between Physical Activity and the Metabolic Syndrome among Type 2 Diabetes Patients in Gaza Strip, Palestine. Ethiop J Health Sci 27: 273-282.
18. El-Khair MA, AbuMustafa AM, Zabut BM (2019) Clinical and Dietary Assessment of Poor Glycemic Control Among Type 2 Diabetic Patients in Gaza Strip, Palestine. J Dia Endo Meta 2: 103.
19. O'Keefe JH, Abuannadi M, Lavie CJ, Bell DS (2011) Strategies for Optimizing Glycemic Control and Cardiovascular Prognosis in patients with Type 2 Diabetes Mellitus. Mayo Clinic proceedings 86: 128-138.

20. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N (2011) Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med 171: 404-410.

21. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ (2014) Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World J Diabetes 5: 444-470.

22. Takao T, Matsuyama Y, Suka M, Yanagisawa H, Kasuga M (2019) Analysis of the duration and extent of the legacy effect in patients with type 2 diabetes: A real-world longitudinal study. J Diabetes Complications 33: 516-522.

23. AbuMustafa A, Yassin M (2017) Clinical and Biochemical Aspects Associated with Diabetic Nephropathy among Type 2 Diabetic Males in Gaza Strip. Int J Med 5: 142-148.

24. Gimeno Orna JA, Blasco Lamarca Y, Campos Gutierrez B, Molinero Herguedas E, Lou Arnal LM (2014) Morbidity and mortality cardiovascular risk in dependence of type 2 diabetes duration. Clin Investig Arterioscler 26: 122-130.

25. Davey M, Atlee C (2011) Inotropic and Cardioprotective Effect of Terminalia Paniculata Roth Bark Extract in Doxorubicin Induced Cardiotoxicity in Rats. Int J Res Ayurveda Pharm 2: 869-875.

26. Ali F, Naqvi SAS, Bismillah M, Wajid N (2016) Comparative analysis of biochemical parameters in diabetic and non-diabetic acute myocardial infarction patients. Indian Heart J 68: 325-331.

27. Gencer B, Rigamonti F, Nanchen D, Klingenberg R, Räber L, et al. (2018) Prognostic values of fasting hyperglycaemia in non-diabetic patients with acute coronary syndrome: A prospective cohort study. Eur Heart J Acute Cardiovasc Care 1: 2048872618777819.

28. Ezeiruaku F (2019) MON-165 The Risk of Developing Cardiovascular Diseases Increases with Age in Type 2 Diabetes Mellitus Patients in Yenagoa, Bayelsa State, Niger Delta Region of Nigeria. J Endocr Soc 3: 165.

29. Fathy SA, Abdel Hamid FF, Zabut BM, Jamee AF, Ali MA, et al. (2015) Diagnostic utility of BNP, corin and furin as biomarkers for cardiovascular complications in type 2 diabetes mellitus patients. Biomarkers 20: 460-469.

30. Yassin MM, Mustafa A, Abujami S, Jaber E (2017) Leptin status and biochemical parameters in type 2 diabetic males from Gaza strip. Annals of Medical and Biomedical Sciences 3: 4-10.

31. Santaguida PL, Don-Wauchope AC, Oremus M, McKelvie R, Ali U, et al. (2014) BNP and NT-proBNP as prognostic markers in persons with acute decompensated heart failure: a systematic review. Heart Fail Rev 19: 453-470.

32. Wang J, Tan GJ, Han LN, Bai YY, He M, et al. (2017) Novel biomarkers for cardiovascular risk prediction. J Geriatr Cardiol 14: 135-150.

33. Peleg A, Ghanim D, Vered S, Hasin Y (2013) Serum corin is reduced and predicts adverse outcome in non-ST-elevation acute coronary syndrome. Eur Heart J Acute Cardiovasc Care 2: 159-165.

34. Mitchell A, Misialek JR, Folsom AR, Duprez D, Alonso A, et al. (2015) Usefulness of N-terminal Pro-brain Natriuretic Peptide and Myocardial Perfusion in Asymptomatic Adults (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 115: 1341-1345.

35. Görmüş U, Ozmen D, Ozmen B, Parildar Z, Ozdoğan O, et al. (2010) Serum N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and homocysteine levels in type 2 diabetic patients with asymptomatic left ventricular diastolic dysfunction. Diabetes Res Clin Pract 87: 51-56.

36. Ikeda N, Nakamura M, Yazaki Y, Ono T, Yamamoto M, et al. (2011) A slightly elevated level of N-terminal pro-brain natriuretic peptide can predict coronary artery disease in a population with normal left ventricular function. Heart vessels 26: 473-479.

37. Chen H, Levine YC, Golan DE, Michel T, Lin AJ (2008) Atrial natriuretic peptide-initiated cGMP pathways regulate vasodilator-stimulated phosphoprotein phosphorylation and angiogenesis in vascular endothelium. J Biol Chem 283: 4439-4447.

38. Shmilovich H, Ben-Shoshan J, Tal R, Afek A, Barshack I, et al. (2009) B-type natriuretic peptide enhances vasculogenesis by promoting number and functional properties of early endothelial progenitor cells. Tissue Eng Part A 15: 2741-2749.

39. Miyashita K, Itoh H, Tsujimoto H, Tamura N, Fukunaga Y, et al. (2009) Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. Diabetes 58: 2880-2892.

40. Tokudome T, Kishimoto I, Yamahara K, Osaki T, Minamino N, et al. (2009) Impaired recovery of blood flow after hind-limb ischemia in mice lacking guanylyl cyclase-A, a receptor for atrial and brain natriuretic peptides. Arterioscler Thromb Vasc Biol 29: 1516-1521.

41. Schirger JA, Grantham JA, Kullo IJ, Jougasaki M, Wennberg PW, et al. (2000) Vascular actions of brain natriuretic peptide: modulation by atherosclerosis and neutral endopeptidase inhibition. J Am Coll Cardiol 35: 796-801.

42. Gruden G, Bruno G, Chaturvedi N, Burt D, Pinach S, et al. (2009) ANTI-HSP60 and ANTI-HSP70 antibody levels and micro/macrovascular complications in type 1 diabetes: the EURODIAB Study. J Intern Med 266: 527-536.