RESEARCH PAPER

The Hyperamylinemia–Inflammation–Coronary Artery Disease Axis in Type 2 Diabetes Mellitus: Exploring Amylin as a Potential Cardiometabolic Therapeutic Target

Shinde Yogita M[1], Badade ZG[2*], Kaul SK[3], Rai Sandeep[4] and Kadam Shilpa[5]

[1]Assistant Professor, Department of Biochemistry, MGM Medical College & Hospital, Kamothe, Navi Mumbai
[2]Professor, Department of Biochemistry, MGM Medical College & Hospital, Kamothe, Navi Mumbai
[3]Professor, Department of CVTS, MGM Medical College & Hospital, Kamothe, Navi Mumbai
[4]Professor, Department of General Medicine, MGM Medical College & Hospital, Kamothe, Navi Mumbai
[5]Professor, Department of Cardiology, MGM Medical College & Hospital, Kamothe, Navi Mumbai
*[*]**Corresponding author:** Badade ZG, Professor, Department of Biochemistry, MGM Medical College & Hospital, Kamothe, Navi Mumbai*
Email: badadezg@gmail.com

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Background: Type 2 Diabetes Mellitus (T2DM) is related with a state of chronic low-grade inflammation and an elevated risk of coronary artery disease (CAD). Human islet amyloid polypeptide (amylin) is co-synthesized, co-stored and co-secreted with insulin and it has a physiological role in glucose homeostasis, but prolonged hyperamylinaemia may cause amyloid aggregation, inflammatory activation and cardiovascular damage. However, its association with glycaemic control, dyslipidaemia, inflammation and CAD is not well known.

Objective: Objectives: To assess the correlation of serum amylin with glycaemic indices, lipid profile, inflammatory biomarkers, insulin resistance and coronary artery disease in patients with Type 2 Diabetes Mellitus and to investigate the potential of amylin as a novel cardiometabolic therapeutic target.

Materials and Methods: This was cross-sectional observational research of 393 adults in three groups: healthy controls (n=131), T2DM without CAD (n=131) and T2DM with angiographically proven CAD (n=131). Fasting blood glucose, postprandial blood glucose, HbA1c, lipid profile, serum insulin, HOMA-IR, QUICKI, serum amylin, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) were estimated by standard biochemical and immunoassays procedures. Correlation tests were performed to investigate the association between serum amylin and cardiometabolic variables on SPSS-24.

Results: In patients with T2DM and T2DM with CAD were considerably elevated Fasting and Postprandial blood glucose, HbA1c, serum insulin, HOMA-IR, total cholesterol, triglycerides, LDL-C, serum amylin, hs-CRP, TNF-α and IL-6 while HDL-C and QUICKI were significantly lower than in healthy controls (all $p<0.001$). Serum amylin showed a strong positive association with BMI, fasting blood glucose, HbA1c, serum insulin, HOMA-IR, total cholesterol, triglycerides, LDL-C and inflammatory biomarkers. Serum amylin had a significant negative correlation with HDL-C and QUICKI. These relationships were higher in patients with T2DM complicated by CAD, suggesting that hyperamylinaemia is closely related to insulin resistance, diabetic dyslipidaemia, systemic inflammation and coronary artery disease.

Conclusion: The present investigation shows that hyperamylinaemia is strongly linked with deterioration of glycaemic control, insulin resistance, diabetic dyslipidaemia and inflammatory activation in individuals with T2DM and especially with those with coronary artery disease. The present study integrates serum amylin with metabolic and inflammatory biomarkers and suggests a Hyperamylinemia–Inflammation–Coronary Artery Disease Axis, providing new clinical evidence that amylin may be an emerging biomarker for cardiometabolic risk stratification and a promising therapeutic target. These data provide a biological justification for further prospective evaluation of non-amyloidogenic amylin analogues, such as Pramlintide and Cagrilintide, as therapeutic approaches to improve cardiometabolic outcomes in patients with Type 2 Diabetes Mellitus.

Keywords: Type 2 Diabetes Mellitus; Serum Amylin; Coronary Artery Disease; Hyperamylinaemia; Inflammation; hs-CRP; TNF-alpha; IL-6; Insulin Resistance; Pramlintide; Cagrilintide.

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**Author for Correspondence: badadezg@gmail.com*

INTRODUCTION

T2DM is a chronic metabolic condition characterized by insulin resistance, increasing beta-cell failure, hyperglycemia and elevated cardiometabolic risk. Cardiovascular disease, especially coronary artery disease (CAD), continues to be a leading source of morbidity and mortality in patients with T2DM. Insulin resistance and hyperglycemia play a role in the development of endothelial dysfunction, dyslipidemia, oxidative stress and accelerated coronary atherosclerosis [1]. Chronic low-grade inflammation is now recognized as an essential physiologic mechanism mediating T2DM and atherosclerotic cardiovascular disease. High-sensitivity C-reactive protein (hs-CRP) and other elevated inflammatory indicators are related with worse vascular outcomes and mortality in high-risk patients with T2DM [2]. Hs-CRP has been demonstrated to have predictive value in individuals with three vessel coronary disease, particularly in those with T2DM, suggesting the role of inflammation in diabetic coronary atherosclerosis [3]. Amylin, commonly known as islet amyloid polypeptide (IAPP), is a 37 amino acid peptide hormone that is co-synthesized, co-stored and co-secreted with insulin from pancreatic β-cells. Under physiological conditions amylin contributes to the control of postprandial glucose levels by delaying stomach emptying, inhibiting glucagon secretion and inducing satiety. However, in insulin resistant (IR) situations the compensatory hyperinsulinemia is accompanied by increased amylin production resulting in Hyperamylinemia. Continued hyperamylinemia may lead to amylin aggregation, β-cell stress and metabolic failure [4]. Recent Indian clinical data have indicated that circulating IAPP levels are considerably higher in patients with T2DM and are positively linked with insulin resistance and inflammatory markers, including hs-CRP, TNF-α, and IL-6 [5]. Moreover, the earlier investigations in diabetic CAD patients revealed that blood amylin level was significantly elevated in T2DM with CAD and significantly associated with inflammatory biomarkers and atherogenic lipid parameters [6]. These findings indicate that hyperamylinemia may be a marker of β-cell stress and may possibly involve inflammatory and atherogenic pathways. Dyslipidemia is another key risk factor for CAD in T2DM. Elevated triglycerides, decreased HDL-C, increased LDL-C, non-HDL-C and changed lipid ratios lead to the production of tiny dense LDL particles, endothelial dysfunction, oxidative stress and plaque progression. In diabetic individuals, atherogenic indices as AIP, CRR, and atherogenic coefficient can offer new information on cardiovascular risk, besides the traditional lipid parameters [7]. The emerging concept of a Hyperamylinemia-Inflammation-Atherosclerosis Axis presents a fresh paradigm to elucidate the crosstalk between β-cell malfunction and systemic inflammation as well as vascular injury in T2DM. Hyperamylinemia may promote inflammatory signaling, increase insulin resistance, contribute to atherogenic dyslipidemia, and consequently hasten coronary atherosclerosis. Amylin-based medicines and amylin receptor modulation have recently attracted fresh attention as prospective cardiometabolic therapy, particularly because amylin analogues can affect appetite, body weight and postprandial glucose regulation [8,9]. However, very few clinical investigations have simultaneously investigated serum amylin, inflammatory biomarkers, insulin resistance, and lipid abnormalities in angiographically confirmed CAD in T2DM patients. Therefore, the current study was designed to analyze the relationship between serum amylin levels and inflammatory load, insulin resistance, dyslipidemia, in T2DM patients with and without CAD and to investigate amylin as a possible therapeutic target for cardiometabolic diseases.

METHODS AND MATERIALS

Study Design and Participants: This hospital based cross-sectional study was conducted in the Department of Biochemistry, General Medicine and Cardiovascular and Thoracic Surgery (CVTS), MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India, from August 2024 to August 2025. Total 393 participants in the age group of 30-60 years were enrolled and equally divided into four groups (n = 131 each) including healthy controls, patients with Type 2 Diabetes Mellitus (T2DM), diagnosed T2DM patients with angiographically confirmed coronary artery disease (CAD).

Inclusion and Exclusion Criteria: Diagnosis of T2DM was based on the American Diabetes Association (ADA) criteria (fasting plasma glucose ≥126 mg/dL and/or HbA1c ≥6.5%). Coronary angiography confirmed CAD cases.

Exclusion criteria: We excluded patients having type 1 diabetes, chronic liver or kidney disease, thyroid disorders, malignancy, acute or chronic inflammatory diseases, autoimmune disorders, infections or other systemic illnesses that could potentially affect inflammatory or metabolic parameters.

Ethical Consideration:

The study protocol was approved by Institutional Ethics Committee, MGM Institute of Health Sciences, Navi Mumbai (Approval No: MGMIHS/RS/2024-25). Written informed consent was obtained from all participants prior to enrolment.

Sample Collection and Biochemical Testing:

Venous blood (8-10 mL) was collected under aseptic conditions after an overnight fast (10-12 h). Fasting and postprandial plasma glucose, HbA1c and lipid profile were estimated using standard laboratory methods. Serum amylin, insulin, high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) were determined by the use of commercially available sandwich ELISA kits according to the manufacturers' instructions. Insulin resistance and insulin sensitivity were assessed by HOMA-IR and QUICKI, respectively. LDL-C and VLDL-C were estimated using Friedewald equation. Statistical Analysis

Data were analyzed with SPSS version 24.0. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Groups were compared using Independent Students t-test and one-way ANOVA, while categorical variables were analyzed using Chi-square test. Appropriate analyses included Pearson correlation, multiple linear regression, and receiver operating characteristic (ROC) curve. A p-value <0.05 was considered statistically significant.

RESULT

Table 1. Baseline Characteristics of Study Participants

Parameter	Control (n=131)	T2DM (n=131)	T2DM+CAD (n=131)	p-value
Age (years)	50.7 ± 5.9	51.2 ± 7.0	52.1 ± 3.7	>0.05
BMI (kg/m²)	21.2 ± 1.65	26.0 ± 2.44	26.6 ± 4.30	<0.001**
Male/Female	59/41	59/41	55/45	>0.05

(** indicates Highly Significant/HS, >0.05 indicates non-significant difference)

Table 2. Comparison of Glycaemic Profile (**HS)

Parameter	Control	T2DM	T2DM+CAD	p-value
Fasting Blood Glucose (mg/dL)	82.9 ± 8.2	175.7 ± 35.3	249.5 ± 35.7	<0.001**
Postprandial Blood Glucose (mg/dL)	105.5 ± 7.4	264.3 ± 49.3	277.5 ± 57.5	<0.001**
HbA1c (%)	4.6 ± 0.5	8.78 ± 2.30	10.6 ± 2.9	<0.001**
Serum Insulin (µU/mL)	6.8 ± 2.1	11.7 ± 3.9	12.9 ± 3.4	<0.001**
HOMA-IR	1.71 ± 0.71	5.11 ± 2.01	6.60 ± 2.60	<0.001**
QUICKI	0.40 ± 0.02	0.31 ± 0.02	0.27 ± 0.01	<0.001**

Table 3. Comparison of Lipid Profile (**HS)

Parameter	Control	T2DM	T2DM+CAD	p-value
Total Cholesterol (mg/dL)	167.7 ± 25.6	202.1 ± 27.7	228.2 ± 25.7	<0.001**
Triglycerides (mg/dL)	95.4 ± 20.2	174.5 ± 15.3	199.6 ± 15.7	<0.001**
HDL-C (mg/dL)	56.8 ± 6.9	42.0 ± 5.6	37.6 ± 3.6	<0.001**
LDL-C (mg/dL)	81.8 ± 18.9	125.1 ± 18.8	154.5 ± 17.9	<0.001**
VLDL-C (mg/dL)	19.1 ± 4.0	34.9 ± 5.3	39.9 ± 3.1	<0.001**

Table 4. Comparison of Serum Amylin and Inflammatory Biomarkers

Parameter	Control	T2DM	T2DM+CAD	p-value
Amylin (pmol/L)	10.68 ± 3.72	21.3 ± 10.5	38.0 ± 12.5	<0.001**
hs-CRP (mg/L)	0.67 ± 0.34	3.44 ± 1.77	9.00 ± 3.80	<0.001**
TNF-α (pg/mL)	11.62 ± 5.00	29.5 ± 4.7	46.3 ± 9.4	<0.001**
IL-6 (pg/mL)	8.01 ± 5.13	19.2 ± 5.2	36.2 ± 10.0	<0.001**

Table 5: Correlation of Serum Amylin with BMI, Glycaemic and Lipid Parameters in Patients with Type 2 Diabetes Mellitus and T2DM with Coronary Artery Disease

Variable	T2DM (r)	T2DM + CAD (r)	p-value
BMI	0.525	0.324	<0.001**
Fasting Blood Glucose	0.428	0.868	<0.001**
HbA1c	0.553	0.868	<0.001**
Serum Insulin	0.871	0.851	<0.001**
HOMA-IR	0.864	0.868	<0.001**
QUICKI	−0.864	−0.868	<0.001**
Total Cholesterol	0.558	0.273	<0.01*
Triglycerides	0.320	0.880	<0.001**
HDL-C	−0.750	−0.790	<0.001**
LDL-C	0.568	0.377	<0.001**

Values represent Pearson's correlation coefficient (r). A positive value indicates a direct association, whereas a negative value indicates an inverse association.

DISCUSSION

The current study showed that the distribution of age and sex was similar in the three study groups, but the body mass index (BMI) was significantly higher in patients with T2DM and T2DM with CAD than in healthy controls (p<0.001) (table no.1). Similar age and sex distribution decreases the chances of demographic confounding factors and suggests that the reported biochemical abnormalities are mainly due to metabolic changes associated with the disease. On the other hand, the significantly higher BMI in the diabetic groups emphasizes the considerable role of obesity in the pathogenesis of insulin resistance, chronic inflammation and coronary artery disease. These data are

in agreement with the 2024 American Diabetes Association Standards of Care which state that obesity is the primary modifiable risk factor for Type 2 Diabetes Mellitus and that excess adiposity accelerates insulin resistance, β-cell dysfunction and cardiovascular consequences [10]. Obesity is a major risk factor for coronary artery disease (CAD) in diabetic patients because of ongoing metabolic and inflammatory problems, according to the 2023 European Society of Cardiology Guidelines [11].

The higher BMI in the present study is also in line with Guo et al., who reported that obese T2DM individuals had a higher inflammatory burden and more severe coronary artery disease than lean subjects. The authors reported that chronic inflammation in obesity causes endothelial dysfunction, vascular damage and progression of atherosclerosis [3]. These results are in line with our results that increasing BMI was associated with the diabetes groups which suggests that obesity may create a pro-inflammatory milieu that promotes cardiovascular problems.

The results can be explained by the fact that adipose tissue is an active endocrine organ that secretes pro-inflammatory cytokines such as TNF-α and IL-6 that stimulate hepatic synthesis of hs-CRP. These inflammatory mediators activate NF-κB and JNK pathways, impair insulin receptor signaling, aggravate insulin resistance and promote endothelial dysfunction [12]. Chronic inflammation also causes oxidative stress, vascular smooth muscle proliferation and plaque instability, all of which are implicated in coronary artery disease.

The present findings are further complemented by the work of Roham et al. who showed that insulin resistance associated with obesity increases the secretory demand on pancreatic β-cells resulting in the compensatory hypersecretion of insulin and its co-secretory peptide, amylin. Prolonged hyperamylinaemia results in aggregation of human islet amyloid polypeptide (hIAPP) with subsequent beta-cell death, the activation of inflammatory pathways and progression of metabolic dysfunction [4]. Thus, obesity might be the first event in the chain linking insulin resistance, hyperamylinaemia and systemic inflammation.

Likewise, Balogh et al demonstrated that the pathogenesis of diabetic cardiovascular disease is characterized by chronic inflammation and oxidative stress induced by obesity through potentiation of endothelial dysfunction, myocardial damage and accelerated atherosclerosis. Experimental studies have also demonstrated the presence of circulating amylin oligomers in pancreatic islets, but also in myocardial tissue where they alter calcium homeostasis, induce oxidative stress and impair cardiac function, thus providing a mechanistic support to the hypothetical hyperamylinemia-inflammation-coronary artery disease axis [13].

Taken together, these results suggest that increased BMI is not merely a demographic feature, but a major upstream cardiometabolic risk factor for insulin resistance, excess amylin production, chronic inflammation and coronary artery disease. Thus, the present study supports the hypothesis that hyperamylinaemia may be an important mechanistic link between obesity, inflammation and cardiovascular complications in T2DM patients.

In the present study it was seen (table no. 2) that the level of glycaemic control gradually declined from healthy controls to T2DM patients and then to T2DM with coronary artery disease (CAD). The T2DM and T2DM with CAD groups revealed considerably higher fasting blood glucose, postprandial blood glucose, HbA1c, serum insulin and HOMA-IR and significantly lower QUICKI (all $p<0.001$). These data suggest a progression of diabetic cardiovascular problems with growing insulin resistance, malfunction of beta-cells and poor management of blood glucose.

The observed increase in fasting and postprandial blood glucose and HbA1c is in agreement with Guo et al. who reported that patients with T2DM with poor glycemic control had significantly higher inflammatory burden and more severe coronary artery disease than patients with better metabolic control [3]. Similarly, the American Diabetes Association Professional Practice Committee stressed that chronic hyperglycaemia continues to be the major cause of diabetes vascular problems by the induction of oxidative stress, endothelial dysfunction and chronic low-grade inflammation [10]. Chronic hyperglycaemia is responsible for the formation of advanced glycation end products (AGEs), activation of the receptor for AGEs (RAGE) and stimulation of the NF-κB signalling pathway, thus increasing the production of TNF-α, IL-6 and hs-CRP, which accelerates the formation of atherosclerotic plaques and coronary artery disease [10,14].

The increased serum insulin and HOMA-IR and decreased QUICKI in the present study are suggestive of severe insulin resistance in diabetic individuals especially those with CAD. These results are similar with Petersen and Shulman who established that insulin resistance is the major metabolic defect in Type 2 Diabetes Mellitus and is highly related with endothelial dysfunction and cardiovascular disease [15]. In the context of insulin resistance, pancreatic β-cells try to compensate by raising the production of both insulin and amylin, as these peptides are generated, stored and secreted simultaneously from the same secretory granules. Thus, chronic hyperinsulinaemia will definitely lead to permanent hyperamylinaemia.

Our findings are consistent with those of Roham et al. who showed that chronic hyperamylinaemia causes aggregation of human islet amyloid polypeptide (hIAPP) which leads to β-cell apoptosis, inflammasome activation, oxidative stress and amplification of inflammatory signaling pathways [4]. Excessive amylin oligomerization has been shown to decrease insulin secretory ability and perpetuate chronic inflammation, suggesting a molecular relationship between insulin resistance and progressive degradation of

glucose homeostasis. Similarly, Despa et al. reported that circulating amylin oligomers accumulate not only in the pancreatic islets but also in the myocardial tissue where they induce calcium dysregulation, mitochondrial dysfunction, oxidative stress, and endothelial injury, ultimately contributing to diabetic cardiomyopathy and coronary artery disease [16]. The findings also give biological evidence for the much lower glycaemic profile found in the T2DM with CAD group in the current investigation and further strengthen the postulated Hyperamylinemia–Inflammation–Coronary Artery Disease Axis.

From a therapeutic point of view, the progressive rise in diabetic profile including insulin resistance and putative hyperamylinaemia found in our study implies that abnormal amylin biology could be an important therapeutic target. Pramlintide, a synthetic, non-amyloidogenic counterpart of amylin, mimics the physiologic activities of amylin by inhibiting postprandial glucagon secretion, slowing stomach emptying, and inducing satiety without the formation of lethal amyloid aggregates as in native human amylin [17]. The association between worsening of glycaemic control and hyperamylinaemia, although not assessed in the present study, provides a strong biological basis for future studies to prospectively assess the effect of early amylin replacement therapy with Pramlintide on chronic inflammation, cardiometabolic homeostasis and possibly the future risk of coronary artery disease in patients with Type 2 Diabetes Mellitus. Persistent hyperglycaemia in uncontrolled diabetic individuals promotes abnormalities in lipid metabolism, making these patients more prone to developing dyslipidaemia and its cardiovascular complications.

The present investigation indicated considerable worsening of lipid profile in patients of T2DM and T2DM with CAD as compared to healthy controls (table no. 3). Total cholesterol, triglycerides, LDL-C, and VLDL-C were significantly elevated, while HDL-C was dramatically lowered in diabetic groups, and the most atherogenic pattern was identified in the T2DM with CAD group ($p<0.001$). These data suggest that in T2DM patients, diabetic dyslipidaemia is aggravated by the presence of coronary artery disease. These results are consistent with Feingold's discovery that patients with T2DM typically present with a distinctive pattern of diabetic dyslipidaemia with increased triglycerides, VLDL-C, atherogenic LDL particles and decreased HDL-C [18]. This lipid anomaly is mostly related to insulin resistance, resulting in increased release of free fatty acids from adipose tissue and increased hepatic synthesis of VLDL. Increased VLDL also promotes enrichment of LDL and HDL particles with triglycerides resulting in the production of tiny dense LDL and fast clearance of HDL. Our findings are also consistent with those of Marx et al. who pointed out in the 2023 European Society of Cardiology [ESC] guidelines that dyslipidaemia is a major contributor to cardiovascular disease in diabetes, with LDL-C and triglyceride-rich lipoproteins being important drivers of atherosclerotic plaque development [11]. Similarly, Hasheminasabgorji et al. [19] observed that dyslipidaemia caused oxidative stress, endothelial dysfunction and activation of inflammatory cytokines leading to the acceleration of atherosclerosis. This is in line with our result of the most unfavourable lipid profile in the T2DM with CAD group. In the context of the postulated hyperamylinemia–inflammation–coronary artery disease axis, diabetic dyslipidaemia may further enhance β-cell stress and amylin production.

Insulin resistance and lipid overload induce compensatory hyperinsulinaemia and because amylin is co-secreted with insulin from pancreatic β-cells, this may promote persistent hyperamylinaemia. Roham et al. indicate that continuous increase of human islet amyloid polypeptide promotes amylin aggregation, β-cell dysfunction, oxidative stress, and inflammatory activation [4]. Thus, the dyslipidaemic pattern reported in the present study could be involved not only in atherosclerosis, but also in pathological amylin amyloidogenesis. Moreover, Vari et al. have stated that amylin dyshomeostasis in obesity and diabetes may lead to inflammation and cardiovascular dysfunction [20]. Thus, the group with T2DM with CAD with elevated triglycerides, VLDL-C, LDL-C and decreased HDL-C may reflect a mixed metabolic-inflammatory state where insulin resistance, lipid toxicity, hyperamylinaemia and vascular inflammation function synergistically to accelerate coronary artery disease.

As seen in Table 4, a gradual and statistically significant elevation in serum amylin, hs-CRP, TNF-α and IL-6 levels was observed from healthy controls to T2DM patients and subsequently to T2DM patients with coronary artery disease (CAD) (all $p<0.001$). In the T2DM with CAD group, the concurrent increase in serum amylin and inflammatory markers implies that hyperamylinaemia is directly related to persistent systemic inflammation and the advancement of diabetic cardiovascular problems[21]. The present work builds on these data with the addition of serum amylin and shows that amylin increases in tandem with inflammatory markers in the development from uncomplicated T2DM to T2DM with CAD. This unexpected observation bolsters the postulated Hyperamylinemia–Inflammation–Coronary Artery Disease Axis, showing that hyperamylinaemia may be an upstream mediator linking metabolic failure and inflammatory activation.

The marked elevation of serum amylin in this study corroborates the observations of Wirth et al., who showed that pathological aggregation of human islet amyloid polypeptide (hIAPP) directly contributes to β-cell injury and that selective neutralization of toxic amylin aggregates preserves β-cell integrity and improves metabolic function in experimental models of Type 2 Diabetes Mellitus [22]. Our findings suggest that increased circulating amylin is not simply a consequence of β-cell malfunction but may actively contribute to disease development through the creation of hazardous oligomeric aggregates.

Likewise, Castillo et al. showed that aggregated human amylin produces endothelial damage, oxidative stress and inflammatory activation of pancreatic microvasculature, followed by increased secretion of pro-inflammatory cytokines and progressive β-cell dysfunction [23]. These discoveries mechanistically complement our findings in which higher serum amylin concentrations were associated with significant increases in hs-CRP, TNF-α and IL-6.

The rise in inflammatory biomarkers identified is also consistent with Guo et al. who found that increased hs-CRP was independently related with severe coronary artery disease in patients with Type 2 Diabetes Mellitus [3]. Donath and Meier have also shown that chronic metabolic stress stimulates the NLRP3 inflammasome and NF-κB signaling pathways resulting in overproduction of TNF-α and IL-6, endothelial dysfunction, vascular inflammation and accelerated atherosclerosis [12]. Persistent inflammatory activation aggravates insulin resistance, which leads to higher secretory demands on β-cells and increased co-secretion of insulin and amylin, creating a vicious cycle of hyperglycaemia, hyperamylinaemia, inflammation and coronary artery disease.

Recent experimental evidence also indicates that abnormal amylin deposition is not confined to pancreatic islets. Oligomers of amylin have been detected in myocardial tissue and coronary microvasculature where they induce mitochondrial dysfunction, calcium dysregulation, oxidative stress, endothelial injury and myocardial fibrosis providing a direct mechanistic link between hyperamylinaemia and cardiovascular injury [24]. These data are in line with the significantly increased serum amylin concentrations seen in the T2DM with CAD group in the present investigation. From a translational standpoint, the current findings suggest abnormal amylin biology as a viable therapeutic target. The non-amyloidogenic molecules Pramlintide and the newer long-acting amylin counterpart Cagrilintide mimic the physiological functions of endogenous amylin, but do not create toxic amyloid aggregates, unlike native human amylin. Experimental studies by Kruse et al. showed that structural alteration of amylin analogues retains metabolic efficacy and eliminates their amyloidogenic potential, giving a promising approach to improve glycaemic regulation and reduce β-cell stress [8]. Although the current cross-section study does not allow us to define therapeutic efficacy or causality, our findings provide a strong biological rationale for future prospective clinical trials to investigate whether early amylin analogue therapy can attenuate inflammatory activation, interrupt the hyperamylinemia-inflammation axis, and ultimately reduce the future risk of coronary artery disease in patients with Type 2 Diabetes Mellitus.

The present investigation established substantial associations (table no. 5) between serum amylin and anthropometric, glycaemic and lipid parameters in individuals with Type 2 Diabetes Mellitus (T2DM) and T2DM aggravated by coronary artery disease (CAD). Serum amylin was significantly positively correlated with BMI, fasting blood glucose, HbA1c, serum insulin, HOMA-IR, total cholesterol, triglycerides and LDL-C. Significant negative correlations were identified with QUICKI and HDL-C. Importantly, these relationships were higher in patients with T2DM and CAD, suggesting that increasing serum amylin mirrors worsening insulin resistance, diabetic dyslipidaemia and cardiovascular risk.

The positive connection of serum amylin with BMI implies that obesity is a major contributor to hyperamylinaemia. Increased free fatty acid flow, adipokine dysregulation and persistent low-grade inflammation from excess adipose tissue contribute to insulin resistance and raise the secretory strain on pancreatic β-cells. Since insulin and amylin are co-synthesized and co-secreted by pancreatic beta-cells, hyperinsulinaemia which is compensatory, necessarily is accompanied by excessive amylin secretion. These findings are in agreement with Wirth et al. who showed that sustained overproduction of human islet amyloid polypeptide (hIAPP) leads to abnormal oligomer formation, β-cell damage and progressive metabolic failure [22].
The substantial positive associations between serum amylin and fasting blood glucose, HbA1c, serum insulin and HOMA-IR and the negative correlation with QUICKI suggest that hyperamylinaemia is a close reflection of poor glycaemic management and growing insulin resistance. This is consistent with Petersen and Shulman where they identified insulin resistance as the main metabolic disturbance leading to β-cell stress and advancement of Type 2 Diabetes Mellitus [15]. Under chronic insulin-resistant circumstances, β-cells secrete more insulin and amylin to preserve glucose homeostasis. However, sustained hyperamylinaemia favours aggregation of hIAPP into hazardous oligomers, which is associated with oxidative stress, inflammasome activation, β-cell death and progressive degradation of glucose metabolism.

The substantial positive correlations of blood amylin with total cholesterol, triglycerides and LDL-C and negative association with HDL-C suggest that hyperamylinaemia is directly related to diabetic dyslipidaemia and elevated atherogenic load. These results are consistent with Feingold who classified diabetic dyslipidaemia as a classic metabolic consequence of insulin resistance, characterised by hypertriglyceridaemia, increased LDL-C and decreased HDL-C [18]. Lipid abnormalities are associated with increased hepatic very-low-density lipoprotein production, oxidative alteration of LDL particles, and endothelial dysfunction that accelerate the formation of atherosclerotic plaques.

The much greater correlations in T2DM with CAD group show that serum amylin is more closely connected with deleterious metabolic and cardiovascular changes with the progression of diabetes complications. Guo et colleagues revealed that in individuals with T2DM, higher inflammatory burden associated with poor glycaemic management was independently related with greater

severity of coronary artery disease [3]. Similarly, Donath and Meier observed that prolonged metabolic stress induced activation of the NLRP3 inflammasome and NF-κB signalling cascades, leading to increased production of TNF-α, IL-6 and other inflammatory mediators, which contribute to the progression of endothelial dysfunction and atherosclerosis [12]. The strong association between serum amylin, insulin resistance and dyslipidaemia revealed in this study further supports the hypothesis that hyperamylinaemia may augment these inflammatory pathways and contribute to progression of coronary artery disease.

This current study further expands on our prior work showing increased inflammatory biomarkers among patients with T2DM exacerbated by CAD [18]. Our previous work has demonstrated the relevance of systemic inflammation in diabetic cardiovascular disease and this study shows that serum amylin is closely associated with obesity, insulin resistance, deterioration of blood sugar levels and atherogenic dyslipidaemia. These results give new clinical evidence for the hypothesized Hyperamylinemia-Inflammation-Coronary Artery Disease Axis, where hyperamylinaemia is the molecular bridge connecting metabolic inefficiency with chronic vascular inflammation and coronary artery disease.

From a translational standpoint, these discoveries have substantial therapeutic implications. Because pathological aggregation is a unique property of native human amylin, non-amyloidogenic analogues of amylin, like Pramlintide and the long-acting equivalent Cagrilintide, are viable treatment strategies. Structural alteration by Kruse et al. abolished the amyloidogenic potential of amylin molecules while preserving their physiological metabolic function [8]. Amylin analogues may halt the hyperamylinemia-inflammation axis before irreparable cardiovascular damage by alleviating postprandial hyperglycaemia, inhibiting glucagon secretion, retarding stomach emptying and decreasing β-cell secretory stress. While the present cross-sectional study cannot establish causality or therapeutic efficacy, the strong correlations observed between serum amylin and multiple cardiometabolic risk factors provide a strong biological rationale for future prospective clinical trials evaluating amylin-based therapies as novel strategies for reducing inflammation and preventing coronary artery disease in patients with Type 2 Diabetes Mellitus.

The present study introduces a clinically integrated perspective in which serum amylin emerges as a potential molecular bridge linking insulin resistance, diabetic dyslipidaemia, chronic inflammation, and coronary artery disease in patients with Type 2 Diabetes Mellitus. By proposing the Hyperamylinemia–Inflammation–Coronary Artery Disease Axis, this study extends current understanding of diabetic cardiovascular pathophysiology beyond conventional glycaemic biomarkers and provides a translational framework for future research evaluating serum amylin as an emerging cardiometabolic biomarker and non-amyloidogenic amylin analogues as potential therapeutic strategies for preventing cardiovascular complications in Type 2 Diabetes Mellitus.

Study Limitations:

This cross-sectional, single-centre study cannot establish causality or long-term cardiovascular outcomes. Additionally, tissue amylin deposition was not assessed. Further multicentre prospective and interventional studies are needed to validate the proposed Hyperamylinemia–Inflammation–Coronary Artery Disease Axis and its therapeutic implications.

Conflict of Interest: The authors declare no conflict of interest.

CONCLUSION

The present study demonstrates that serum amylin concentrations increase progressively from healthy individuals to patients with Type 2 Diabetes Mellitus (T2DM) and further to those with T2DM complicated by coronary artery disease (CAD). Hyperamylinaemia was significantly associated with worsening glycaemic control, insulin resistance, diabetic dyslipidaemia, and systemic inflammation, indicating that serum amylin closely reflects the metabolic and inflammatory disturbances underlying diabetic cardiovascular disease.

Importantly, the present findings extend our previous observations on inflammatory biomarkers by integrating serum amylin with glycaemic, lipid, and inflammatory parameters into a unified Hyperamylinemia–Inflammation–Coronary Artery Disease Axis. This integrated approach provides novel clinical evidence that hyperamylinaemia may represent a mechanistic bridge linking β-cell dysfunction, chronic inflammation, and atherosclerotic cardiovascular disease in patients with T2DM.

The strong association of serum amylin with multiple cardiometabolic risk factors suggests that amylin has potential utility not only as an emerging biomarker for cardiovascular risk stratification but also as a promising therapeutic target. These findings provide a biological rationale for future prospective and interventional studies evaluating non-amyloidogenic amylin analogues, such as Pramlintide and Cagrilintide, as potential strategies to interrupt the hyperamylinemia–inflammation axis and improve cardiometabolic outcomes in patients with Type 2 Diabetes Mellitus.

To our knowledge, this study is among the first to clinically integrate serum amylin, inflammatory biomarkers, glycaemic indices, and lipid abnormalities into a comprehensive mechanistic framework linking hyperamylinaemia with coronary artery disease. These findings provide a strong foundation for future translational research exploring amylin-targeted interventions as a novel approach to diabetic cardiovascular prevention.

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