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ALTERATION IN PLATELET PYRUVATE KINASE ISOENZYME (PKM1/PKM2) EXPRESSION IN CORONARY ARTERY DISEASE AND ISCHEMIC STROKE: A PROSPECTIVE OBSERVATIONAL STUDY OF CLINICAL PROFILE AND PLATELET METABOLIC ADAPTATION

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ABSTRACT

Background: Platelets play a key role in arterial thrombosis, causing acute myocardial infarction (AMI) and ischemic stroke. The low-activity dimeric form of pyruvate kinase M2 (PKM2) is involved in mediating a shift in the energy metabolism of activated platelets from oxidative phosphorylation to aerobic glycolysis as compared to PKM2. This balance between the two isoforms has never been investigated in platelets from patients with cardiovascular disease.

Methods: This prospective observational study compared the expression of platelet PKM1 and PKM2 by immunoblotting in 12 patients with acute MI or acute ischemic stroke (cases) and 12 controls. Clinical profile, anthropometric parameters, and fasting biochemical variables (HbA1c, lipid profile) were collected, and correlations between the expression of platelet PKM1 and PKM2 were assessed.

Results: Mean PKM1 expression was slightly higher in cases (0.94 ± 0.85) compared with controls (0.55 ± 0.53); however, the difference was not significant ($p = 0.19$). Mean PKM2 expression was slightly lower in cases (1.62 ± 1.11) compared with controls (2.36 ± 1.56). PKM1 correlated positively with HbA1c, and PKM2 correlated negatively with HbA1c and with fasting LDL cholesterol.

Conclusions: This reciprocal switch to higher expression of PKM1 and lower expression of PKM2 was seen in the platelets of CAD and stroke patients, and was correlated with glycaemic and lipid risk markers. This imbalance in the expression of PK protein in platelets could be one of the metabolic adaptations that connects the cardiometabolic risk factors to platelet hyperactivity and thrombotic risk in cardiovascular diseases.

KEYWORDS: *platelets; pyruvate kinase M2; aerobic glycolysis; coronary artery disease; ischemic stroke; platelet metabolism*

1. INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality in India and worldwide.[1] Ischemic heart disease and stroke together account for more than 80% of all CVD-related deaths in India.[2] Acute myocardial infarction (MI) and ischemic stroke share a common pathophysiological basis, and acute MI is regarded as one of the recognised aetiologies of ischemic stroke.[3] When a probable cardiac source is identified, such strokes are termed cardio-embolic, with intra-cardiac thrombi related to atrial fibrillation or MI among the most important sources.[4] Because the great majority of left ventricular thrombi arise in anteriorly located infarctions, anticoagulation strategies have historically targeted patients with anterior-wall MI.[5,6] More recently, however, the significance of anterior-wall MI—and hence of left ventricular thrombus—as an independent risk factor for stroke has been called into question.[7] The widespread use of thrombolytic therapy and aspirin for acute MI has not reduced the incidence of left ventricular thrombus formation, although it may have altered the subsequent risk of embolism.[8] Patients who develop ischemic stroke after acute MI have greater morbidity and higher short- and long-term mortality than those without stroke.[9]

Platelets are the pivotal cellular effectors of arterial thrombosis underlying both MI and ischemic stroke.[10] In an intact vasculature platelets remain quiescent, but upon a breach in endothelial integrity they adhere to exposed sub-endothelial collagen through cell-surface receptors, change shape, aggregate through a fibrinogen bridge linking activated integrins, and degranulate, thereby recruiting further platelets and amplifying the local thrombotic response.[11]

These processes are energy-intensive, and activated platelets must adapt their metabolism to sustain shape change, integrin activation, aggregation and granule secretion, often under conditions of relative hypoxia and nutrient restriction within a densely packed thrombus.[12] Metabolic energy is required by platelets at every stage of aggregation and secretion,[13] and although platelets possess functional mitochondria, their reserve capacity for

oxidative phosphorylation is limited relative to their capacity for glycolytic ATP generation.[14] Upon activation, glucose availability increases through translocation of the GLUT3 transporter to the plasma membrane,[15] supporting a marked and sustained rise in glycolytic flux that outlasts the transient rise in oxidative phosphorylation.[16] The resulting aerobic glycolysis accelerates flux through the pentose phosphate pathway, generating NADPH that fuels NADPH-oxidase-dependent reactive-oxygen-species production and, in turn, activation of the platelet integrin αIIbβ3.[17]

This metabolic switch is mediated in part by functional inhibition of pyruvate kinase M2 (PKM2), one of four pyruvate kinase isoenzymes expressed in a tissue-specific manner according to the metabolic demands of each tissue.[18] PKM1 and PKM2 are generated from a single PKM gene by alternative splicing.[19] PKM1 exists constitutively as a high-activity tetramer, whereas PKM2 can adopt either a high-activity tetrameric or a low-activity dimeric conformation, and it is this low-activity dimeric state that favours aerobic glycolysis.[20] This glycolytic phenotype is analogous to the Warburg effect described in proliferating and neoplastic cells, in which PKM2 expression likewise supports biosynthetic flux at the expense of maximal ATP yield.[21]

Beyond platelets, altered pyruvate kinase isoform expression has been implicated in the pathobiology of several cardiovascular conditions. In human coronary atherosclerotic plaques, PKM2 is highly expressed, almost exclusively in CD68 positive cells, establishing a link between metabolic and inflammatory dysfunctions of coronary artery disease (CAD), and connecting proliferating endothelial cells to a proglycolytic shift in expression, driven by a predominance of the PKM2 isoform over the PKM1 under hypoxic, nutrient poor conditions, resembling those of tumour cells. Platelet endothelial denudation is associated with platelet granule content release as well as mitogenic factors, which independently play a role in atherogenesis and lead to the presence of serologic markers of platelet activation that are characteristic of acute coronary syndromes, and which are among the first and most persistent responses to endothelial denudation. [27,28]

Reduced PKM1 expression has been reported in failing human and murine hearts, suggesting that PKM1 helps sustain a homeostatic metabolic response under haemodynamic stress.[22] A proglycolytic shift from PKM1 to PKM2 predominance accompanies right-ventricular fibrosis in experimental pulmonary hypertension.[23] Proliferating endothelial cells rely on PKM2 for growth and migration under hypoxic, nutrient-poor conditions in a manner reminiscent of tumour cells, and depend on this isoform to maintain vascular integrity.[24] Within human coronary atherosclerotic plaques, macrophages overexpress PKM2, which localises almost exclusively to CD68-positive cells and bridges metabolic and inflammatory dysfunction in coronary artery disease (CAD).[25]

Platelet adhesion to the sub-endothelium is among the earliest and most consistent responses to endothelial denudation, preceding leukocyte recruitment by many hours.[26] Activated platelets release stored mediators, including platelet factor 4, into the sub-endothelial space; this release of granule contents and mitogenic factors is central both to the platelet contribution to atherogenesis and to the serologic markers of platelet activation observed in acute coronary syndromes. [27,28]

Despite this body of evidence implicating pyruvate kinase isoform switching in cardiovascular pathology at the level of the myocardium, vasculature and macrophage, no prospective study has directly compared the relative expression of PKM1 and PKM2 in the platelets of patients with cardiovascular disease against that of healthy controls, nor related this expression to clinical and biochemical risk markers. We hypothesised that an imbalance in platelet PKM splice-isoform expression could underlie platelet hyperactivity and increased thrombotic risk in patients with CAD and ischemic stroke. The present study was therefore designed to determine the relative expression of PKM1 and PKM2 proteins in the platelets of patients with acute coronary artery disease or acute ischemic stroke as compared with age- and sex-matched healthy controls, and to explore correlations between this expression and clinical and metabolic parameters.

2. MATERIALS AND METHODS

2.1 Study design, setting and ethics

This prospective observational study was conducted jointly in the Department of General Medicine and the Department of Biochemistry between August 2019 and December 2021. The study protocol and informed consent documentation were approved by the Institutional Ethics Committee, and written informed consent was obtained from every participant prior to enrolment.

2.2 Study population

Individuals over 18 years of age of both the gender with acute MI or acute ischemic stroke were recruited from the outpatient department, while twelve age and sex matched healthy volunteers were recruited as controls. Acute MI (types 1, 2 and 3) was defined as acute myocardial injury with clinical evidence of myocardial ischemia and a rise and/or fall in cardiac troponin levels with at least one level above the 99th percentile, plus at least one of: symptoms of myocardial ischemia; new ischemic ECG changes; the presence of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality of ischemic pattern; or angiographic evidence of a coronary thrombus. Acute ischemic stroke was defined as brain cell death caused by ischemia, with definite focal

neurological dysfunction and with neuropathological, neuro-imaging and/or clinical evidence of permanent injury, according to the updated definition from the American Heart Association/American Stroke Association. [29] The following were excluded from the cases: age < 18 years, alcoholism or drug abuse, and refusal of consent. The healthy controls were those who were under 18 years of age, who had a history of alcoholism or drug abuse, who had had a thrombo-embolic event within the past 12 months, who had taken antiplatelet or anticoagulant drugs within the last 4 weeks, or who had an acute inflammatory condition.

2.3 Sample collection and platelet preparation

Ten millilitres of peripheral venous blood was drawn under aseptic precautions from each participant into vials containing citrate-phosphate-dextrose-adenine anticoagulant. Platelet-rich plasma (PRP) was obtained by brief centrifugation at 180 × g for 10 minutes and incubated with 1 mM acetylsalicylic acid for 15 minutes at 37 °C to arrest ex-vivo activation. Platelets were then sedimented by centrifugation at 600 × g for 10 minutes following addition of 5 mM EDTA, washed in Buffer-A (20 mM HEPES, 138 mM NaCl, 2.9 mM KCl, 1 mM $MgCl_2$, 0.36 mM NaH_2PO_4, 1 mM EGTA, 5 mM glucose; pH 6.4), and finally re-suspended in Buffer-B (identical to Buffer-A but without EGTA; pH 7.4). Platelet counts were determined on a Beckman Coulter cell counter, and the final suspension was adjusted to 3.0×10^8 cells/mL. All steps were performed at room temperature under sterile conditions, with precautions taken to maintain platelets in the resting state.

2.4 Immunoblotting

Platelet proteins were resolved on 10% SDS-polyacrylamide gels and electrophoretically transferred to polyvinylidene fluoride (PVDF) membranes using a semi-dry blotting system (Bio-Rad). Membranes were blocked with 5% non-fat dry milk in Tris-buffered saline containing 0.05% Tween-20 (TBST) for one hour at room temperature, and then incubated overnight at 4 °C with primary antibodies against PKM2 (1:1000), PKM1 (1:1000) or β-actin (1:5000), followed by three 5-minute washes in TBST. Membranes were subsequently incubated with HRP-conjugated anti-rabbit IgG secondary antibody for one hour, washed, and developed using an enhanced chemiluminescence substrate. Blots were imaged on a BioSpectrum 800 multispectral imaging system (UVP) and band intensities quantified using Vision Works LS software (UVP), with PKM1 and PKM2 signal normalised to the corresponding β-actin loading control for each sample.

2.5 Statistical analysis

Data were entered into Microsoft Excel and analysed using GraphPad Prism (version 8.4.0). Continuous variables are summarised as mean ± standard deviation and categorical variables as counts and percentages. Group means were compared using the unpaired Student's t-test. Pearson correlation coefficients (r) were calculated to assess bivariate associations between platelet PKM1, PKM2 and clinical-biochemical variables. A two-tailed p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics of the study population

Twelve cases and twelve controls, matched for age and sex, were enrolled (Table 1). The mean age of cases (50.75 ± 8.55 years) was comparable to that of controls (47.75 ± 8.52 years), and the gender distribution was identical between groups (58.3% male, 41.7% female in each). A family history of cardiovascular disease was present in 33.3% of cases and 25.0% of controls, and a history of smoking was more frequent among cases (41.7%) than controls (8.3%). None of the participants in either group reported alcohol use. Among the cases, 66.7% presented with ischemic stroke and 33.3% with coronary artery disease.

Table 1. Baseline demographic and clinical characteristics of cases and controls

Variable	Cases (n = 12)	Controls (n = 12)
Mean age, years (± SD)	50.75 ± 8.55	47.75 ± 8.52
Male sex, n (%)	7 (58.3%)	7 (58.3%)
Female sex, n (%)	5 (41.7%)	5 (41.7%)
Family history of CVD, n (%)	4 (33.3%)	3 (25.0%)
History of smoking, n (%)	5 (41.7%)	1 (8.3%)
History of alcohol use, n (%)	0 (0%)	0 (0%)
Ischemic stroke, n (%)	8 (66.7%)	—
Coronary artery disease, n (%)	4 (33.3%)	—

3.2 Clinical and biochemical parameters

Cases had higher mean systolic and diastolic blood pressure, higher body mass index (BMI), higher HbA1c, and higher fasting LDL cholesterol and triglycerides than controls, while mean platelet count was numerically lower in cases (Table 2). These findings are consistent with the expected cardiometabolic risk profile of patients with established coronary artery disease or ischemic stroke.

Table 2. Mean clinical, anthropometric and biochemical parameters, and platelet PKM1/PKM2 expression, in cases and controls

Parameter	Cases (Mean ± SD)	Controls (Mean ± SD)
Systolic blood pressure (mm Hg)	137.83 ± 17.57	121.83 ± 9.32
Diastolic blood pressure (mm Hg)	84.00 ± 7.48	78.17 ± 4.78
BMI (kg/m²)	28.43 ± 2.77	23.73 ± 1.81
Platelet count (×10³/μL)	207.00 ± 42.75	230.83 ± 61.38
HbA1c (%)	7.13 ± 1.07	5.94 ± 0.36
Fasting LDL cholesterol (mg/dL)	129.33 ± 30.47	73.00 ± 12.00
Fasting triglyceride (mg/dL)	171.08 ± 45.77	117.25 ± 15.86
Platelet PKM1 (relative to β-actin)	0.94 ± 0.85	0.55 ± 0.53
Platelet PKM2 (relative to β-actin)	1.62 ± 1.11	2.36 ± 1.57

3.3 Platelet PKM1 and PKM2 expression

Representative immunoblots for PKM1, PKM2 and the β-actin loading control in platelets from cases and controls are shown in Figure 2. The mean relative expression of PKM1 (normalised to β-actin) was higher in cases (0.9427) than in controls (0.5525), whereas the mean relative expression of PKM2 was lower in cases (1.6245) than in controls (2.3617) (Table 2, Figure 1). Although this pattern was consistent with a reciprocal shift toward the constitutively active PKM1 isoform and away from the pro-glycolytic PKM2 isoform in the platelets of cases, neither difference reached statistical significance on unpaired Student's t-test (p = 0.19 for both comparisons), reflecting the limited sample size of this pilot cohort.

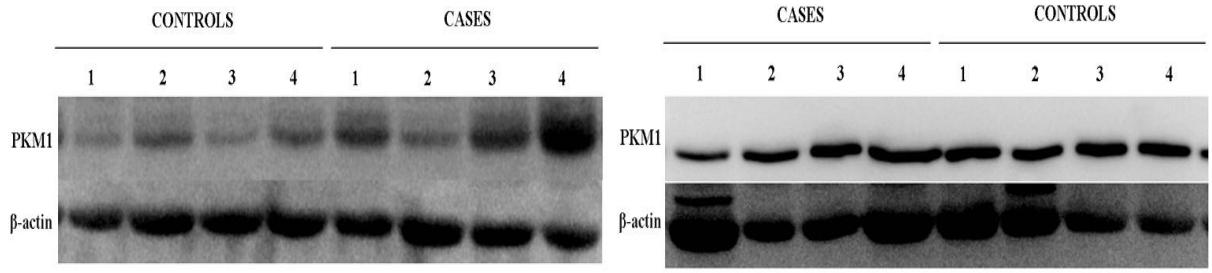


Figure 1. Relative platelet expression of PKM1 (left) and PKM2 (right), normalised to β-actin, in controls versus cases. Each point represents one participant; horizontal bars indicate mean ± SEM. PKM1 was numerically higher and PKM2 numerically lower in cases than controls (unpaired t-test, p = 0.19 for both).

3.4 Correlation of platelet PKM1/PKM2 with clinical and biochemical variables

Pearson correlation analysis across the study cohort demonstrated a statistically significant positive correlation between platelet PKM1 expression and HbA1c (r = 0.5570, p = 0.0047), and a significant negative correlation between PKM2 expression and HbA1c (r = −0.4516, p = 0.0267) (Table 3, Figure 3A–B). PKM2 also correlated negatively with fasting LDL cholesterol (r = −0.4284, p = 0.0367) (Figure 3C), while PKM1 and PKM2 expression were inversely correlated with one another (r = −0.6148, p = 0.0014) (Figure 3D). Additional expected physiological correlations were observed: fasting LDL correlated positively with HbA1c (r = 0.5990, p = 0.0200), systolic blood pressure correlated positively with BMI (r = 0.4716, p = 0.0200), HbA1c correlated positively with BMI (r = 0.6928, p = 0.0002), and BMI correlated positively with fasting LDL (r = 0.5781, p = 0.0031).

Table 3. Pearson correlation coefficients (r) and two-tailed significance (p) among platelet PKM1, PKM2 and clinical/biochemical variables

Variable	PKM1	PKM2	BMI	SBP	HbA1c	Fasting LDL
PKM1 (r)	1	−0.6148	0.1066	0.1879	0.5570	0.3767
PKM1 (p)	—	0.0014	0.6201	0.3793	0.0047	0.0696
PKM2 (r)	−0.6148	1	−0.1934	−0.1894	−0.4516	−0.4284
PKM2 (p)	0.0014	—	0.3651	0.3754	0.0267	0.0367
BMI (r)	0.1066	−0.1934	1	0.4716	0.6928	0.5781

BMI (p)	0.6201	0.3651	—	0.0200	0.0002	0.0031
SBP (r)	0.1879	−0.1894	0.4716	1	0.2998	0.2331
SBP (p)	0.3793	0.3754	0.0200	—	0.1547	0.2730
HbA1c (r)	0.5570	−0.4516	0.6928	0.2998	1	0.5990
HbA1c (p)	0.0047	0.0267	0.0002	0.1547	—	0.0020
Fasting LDL (r)	0.3767	−0.4284	0.5781	0.2331	0.5990	1
Fasting LDL (p)	0.0696	0.0367	0.0031	0.2730	0.0020	—

r, Pearson correlation coefficient; p, two-tailed significance; SBP, systolic blood pressure.

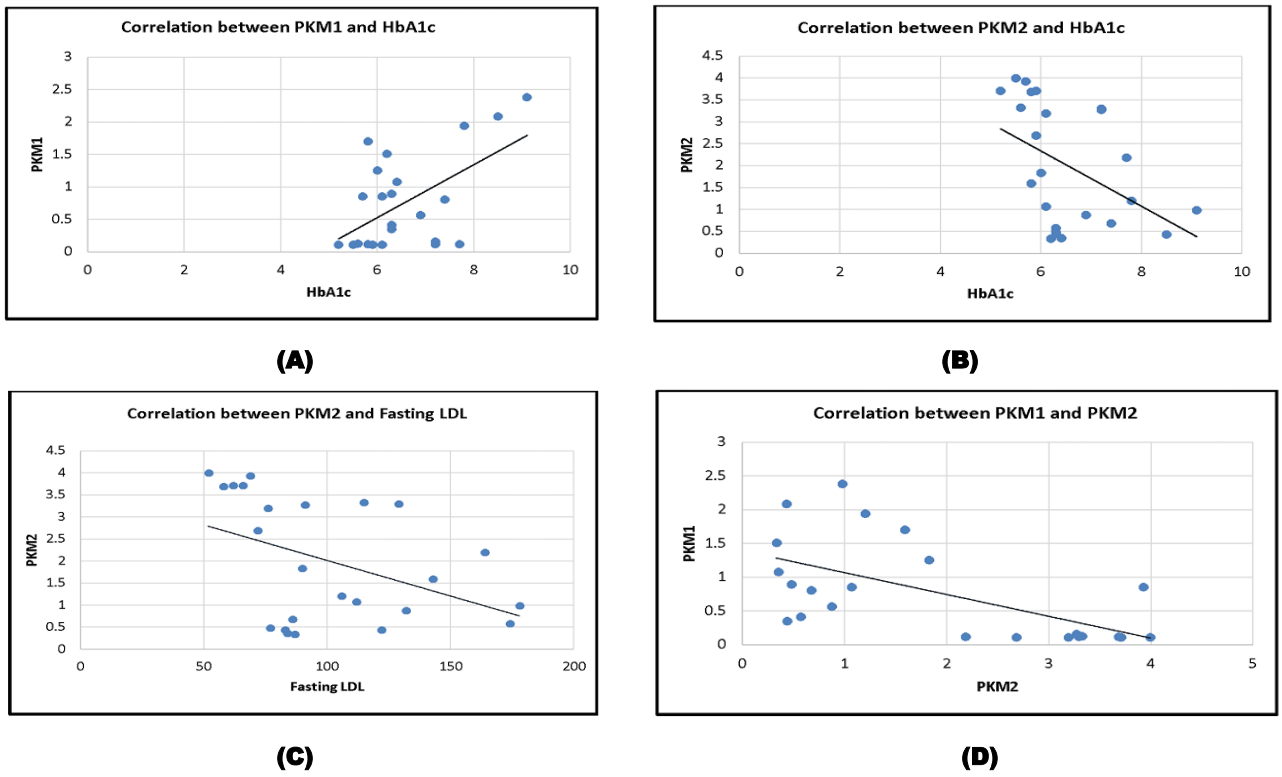


Figure 3. Scatter plots of statistically significant correlations. (A) PKM1 vs HbA1c (r = 0.557, p = 0.0047). (B) PKM2 vs HbA1c (r = −0.452, p = 0.027). (C) PKM2 vs fasting LDL cholesterol (r = −0.428, p = 0.037). (D) PKM1 vs PKM2 (r = −0.615, p = 0.0014).

4. DISCUSSION

This prospective observational study is, to our knowledge, the first to directly compare the relative platelet expression of the two pyruvate kinase splice isoforms, PKM1 and PKM2, between patients with cardiovascular disease (acute MI or acute ischemic stroke) and healthy controls. We found that platelet PKM1 expression was numerically higher, and PKM2 expression numerically lower, in cases than in controls, and that this reciprocal pattern correlated significantly with two established cardiometabolic risk markers, HbA1c and fasting LDL cholesterol.

The functional inhibition and dimerisation of PKM2 that drives aerobic glycolysis is required acutely for platelet aggregation, granule secretion and thrombus formation.[30] Based on this mechanism alone, one might have anticipated higher rather than lower steady-state PKM2 expression in the platelets of patients with established thrombotic cardiovascular disease. Our finding of relatively higher PKM1 and lower PKM2 in cases may therefore reflect a chronic transcriptional or megakaryocyte-level adaptation that is distinct from the acute, activation-triggered functional switch of PKM2 described in isolated platelets. A parallel dissociation between chronic isoform expression and acute functional switching has been described in the heart, where PKM1 is paradoxically reduced rather than increased in chronically failing myocardium despite the tissue's increased reliance on glycolysis under haemodynamic stress, and in the right ventricle in pulmonary hypertension, where sustained pressure overload drives a shift toward PKM2 predominance rather than away from it.[31,32] Platelets, as anucleate fragments inherited from megakaryocytes, may likewise carry forward a disease-associated splicing signature established at the megakaryocyte level rather than one generated de novo with each activation event. [33]

The observation that platelet PKM2 was also reduced in our cases is superficially at variance with reports of PKM2 overexpression in macrophages within human coronary atherosclerotic plaques, where PKM2 bridges glycolytic and

inflammatory signalling and localises predominantly to CD68-positive cells.[34] This apparent discrepancy underscores that pyruvate kinase isoform regulation is likely to be cell-type- and context-specific: the same disease process, coronary atherosclerosis, may up-regulate PKM2 in resident plaque macrophages while a distinct pattern operates in circulating platelets and in endothelial cells, where PKM2 instead supports proliferative, barrier-maintaining functions.[24,35] Direct comparison of PKM1/PKM2 regulation across these different vascular cell compartments in the same patients would help clarify whether they represent independent or coordinated responses to the same atherothrombotic stimulus.

The strong positive correlation between PKM1 and HbA1C, and the strong negative correlations between PKM2 and both HbA1C and fasting LDL cholesterol, indicate that the relative expression of the two isoforms of pyruvate kinase in platelets is influenced by glycaemic and lipid status, both of which are known, modifiable risk factors for coronary artery disease and ischemic stroke. [36] This suggests that switching of platelet PK isoenzymes may not only be a marker of thrombotic disease but also a mechanism by which dysglycaemia and dyslipidaemia might be reflected as changes in platelet metabolic behaviour and, perhaps, thrombotic risk. Our clinical and biochemical measurements are internally valid as we found the expected physiological correlation between BMI, systolic blood pressure, HbA1c and fasting LDL which is consistent with the known clustering of cardiometabolic risk factors in this population.

From a clinical standpoint, current antiplatelet therapy for secondary prevention after MI or ischemic stroke remains imperfect. Aspirin resistance is well documented among patients with cardiovascular disease, and standard platelet-function assays used to monitor antiplatelet therapy each capture only part of the complexity of platelet biology. [37,38] For secondary stroke prevention specifically, current American Heart Association/American Stroke Association guidelines [39] recommend dual antiplatelet therapy only for a limited early window after minor stroke or high-risk transient ischaemic attack. Pooled evidence indicates this approach reduces early recurrent ischaemic events when started early and continued briefly, but confers no added efficacy and increased bleeding risk when used for longer or started later; even potent, direct-acting P2Y12 inhibitors such as ticagrelor have failed to outperform aspirin for the prevention of major vascular events after acute cerebral ischaemia.[40,41] Newer antiplatelet strategies under investigation continue to target aggregation pathways rather than platelet energy metabolism itself, and all currently approved agents remain constrained by a trade-off between antithrombotic efficacy and bleeding risk.[42]

An alternative strategy is the use of small molecules that modulate platelet energy metabolism. Diarylsulphonamide-58, dichloroacetate and dehydroepiandrosterone (DHEA) all affect the flux through aerobic glycolysis and/or the pentose-phosphate pathway, and all inhibit agonist-induced platelet aggregation and granule secretion, delaying the formation of a thrombus in animal models of arterial injury, and DHEA has been associated with reduced cardiovascular mortality in observational cohorts; small-molecule activators that lock PKM2 into its high-activity tetrameric conformation have been developed and validated in other disease contexts. [43-45] Our finding that platelet PKM2 is already reduced, and PKM1 relatively increased, in patients with established cardiovascular disease adds a further layer of complexity to the rationale for such metabolic modulators, and highlights the importance of directly characterising basal pyruvate kinase isoform expression in the target patient population before extrapolating from mechanistic studies in isolated, acutely activated platelets.

There are several limitations to this study. The number of cases and controls (12 in each group) was small, which reduced the power to detect the observed difference in expression of PKM1/PKM2 between the two groups as significant, despite a consistent trend in the direction of the difference; this is a recognised limitation of pilot translational studies of this type, and our between-group comparison must be considered hypothesis-generating rather than confirmatory. Due to the cross-sectional design, conclusions about causality and the temporal sequence of isoform switching in relation to the index vascular event cannot be drawn. The cases were well matched with controls for age and sex but had a higher prevalence of smoking and a more unfavourable metabolic profile, which is consistent with their diagnosis, and may have influenced the platelet metabolic phenotype, independent of or in addition to, the vascular event itself. The study included patients with MI and with ischemic stroke, two related but not identical types of MI, and the study was not designed to analyze these subgroups separately. Lastly, the expression of PKM1/PKM2 was evaluated by immunoblotting, and the association of this expression with functional assays of platelet reactivity, such as light-transmittance aggregometry or flow-cytometric expression of P-selectin, would complement the biological interpretation of our results.

Future studies with larger, adequately powered cohorts, incorporating functional platelet aggregation assays alongside PKM1/PKM2 quantification, and comparing subtypes of cardiovascular disease (MI versus ischemic stroke) and comorbidity strata (diabetic versus non-diabetic, dyslipidaemic versus normolipidaemic), are needed to confirm and extend these preliminary observations and to clarify whether platelet pyruvate kinase isoform expression could serve as a biomarker of platelet reactivity or as a target for metabolically directed antithrombotic therapy.

5. CONCLUSION

Patients with ischemic stroke or coronary artery disease had higher platelet expression of PKM1 and lower expression of PKM2 than age- and sex-matched healthy controls, and this was significantly associated with HbA1c and fasting LDL cholesterol. The relative expression of the two splice isoforms of pyruvate kinase in platelets may be one of the

molecular metabolic changes in patients with cardiovascular disease, which is related to established cardiometabolic risk factors and platelet hyperactivity. Detailed characterization of this pathway in larger, properly powered cohorts may guide future strategies for clinical risk stratification and for metabolically targeted anti-thrombotic therapy, especially in resource-poor countries like India where the mortality and morbidity of coronary artery disease and ischemic stroke is high.

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