Abbas *et. al.,* Babcock Univ. Med. J.2026 9(3):142-150
https://doi.org/10.38029/babcockuniv.med.j..v9i3.1499
eISSN: 2756-4657

REVIEW ARTICLE OPEN ACCESS

Decoding Paediatric Type 1 Diabetes Through the Gut Immune Pancreas Axis: Integrated Roles of I-FABP, Platelet-Activating Factor, and Micrornas: A Narrative Review

Gut-immune-pancreas axis in paediatric T1D

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Submitted: 4th January 2025
Accepted: 8th April 2026
Published: 30th September 2026

ID: Orcid ID

Abstract

Background: Type 1 diabetes (T1D) in children develops when genetic risk, environmental triggers, and the immune system join forces to destroy the pancreatic beta cells. Lately, research is pointing toward trouble in the gut. When the intestinal barrier gets damaged, and the gut microbiota goes off-balance, this can kickstart or worsen islet autoimmunity and early vascular problems.

Main body: This narrative takes a close look at three groups of biomarkers, intestinal fatty acid binding protein (I-FABP), platelet-activating factor (PAF), and certain microRNAs (miRNAs), and makes the case for viewing them together instead of in isolation. High I-FABP means the enterocytes are getting hurt and the gut lining isn't holding up, which points to a leaky gut barrier.

Conclusion: The integrated gut-immune-pancreas axis model presented here may facilitate the identification of novel therapeutic targets and early intervention strategies to prevent or delay paediatric T1D. Prospective validation of these biomarkers in African and other under-represented populations is urgently needed.

Keywords: Type 1 diabetes, Intestinal fatty acid binding protein, Platelet-activating factor, MicroRNA, Gut barrier, Paediatric endocrinology

Background

Type 1 diabetes (T1D) remains one of the most common chronic endocrine disorders in children and adolescents. Worldwide, an estimated 8.4 million people live with T1D, of whom 1.5 million are under 20 years of age (1). Despite advances in insulin formulations and glucose monitoring, most young people do not achieve recommended glycaemic targets, leading to significant lifelong morbidity (2). Most patients have already lost 70–90% of their beta-cell functional mass by the time of clinical diagnosis (3). Circulating islet autoantibodies (IAA, GADA, IA-2, ICA) are present in most newly diagnosed children, but they reflect ongoing autoimmunity rather than its root causes (3).

T1D doesn't have a straightforward explanation. There's family history, HLA and non-HLA genes, outside triggers, food, viruses, and even the gut microbiome; everything's involved (4, 5, 6). Over the last ten years, people have started to see the gut microbiota as a key player in immune tolerance. Dysbiosis, lower microbial diversity and not enough bacteria making short-chain fatty acids, show up both before and after islet autoimmunity kicks in (7). When the microbiome changes, the gut lining weakens, permeability goes up, and autoimmune problems can start from molecular mimicry or straight-up immune activation (8).

On this backdrop, this review pulls together three biomarker classes that have usually been studied separately but are tied together by underlying

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mechanisms: I-FABP as a marker for enterocyte injury, PAF as a pro-inflammatory lipid, and miRNAs as epigenetic regulators. The main idea: these all feed into a gut-immune-pancreas axis, which can help explain how gut barrier issues drive the shift from being at risk (autoantibody positive) to getting full-blown T1D in kids. For this review, PubMed, Scopus, and Google Scholar were searched up to March 2026 using: "type 1 diabetes AND children," "I-FABP," "platelet activating factor," and "microRNA AND gut barrier." Only English articles with full text were included. Studies in children were prioritised, but adult and basic research also made the cut.

Main text

Gut barrier injury and I-FABP in paediatric T1D

The intestinal barrier is a moving target, it is made up of the gut microbiota, a mucus layer, enterocytes, tight junction (TJ) proteins, and gut-associated lymphoid tissue (9). The tight junctions—built from proteins like claudins, occludin, and zonula occludens 1 (ZO-1)- keep the space between cells sealed off, letting small things through while blocking antigens and microbial nasties (10). But when tight junctions break down, the gut gets leaky, and then stuff like bacterial lipopolysaccharide (LPS) and other inflammatory molecules flood the bloodstream (11).

Children with islet autoimmunity or T1D often show increased gut permeability and an imbalanced microbiome (12). There's a pro-inflammatory storm in the small intestine; more IFN-γ, IL-1α, and IL-4-producing cells appear in T1D patients (13). Moreover, lymphocytes targeting beta-cell antigens express the gut-homing receptor α4β7, directly linking intestinal immune activation to pancreatic autoimmunity (13). Because intestinal biopsies are invasive, non-invasive permeability tests and serum biomarkers have become attractive alternatives.

Intestinal fatty acid-binding protein (I-FABP; FABP2) is a 14–15 kDa cytosolic protein abundantly expressed in mature enterocytes of the small intestine (14). Its physiological role is to bind and transport long-chain fatty acids. When enterocytes are damaged by ischaemia, inflammation, or toxic injury, I-FABP is rapidly released into the bloodstream, where it can be measured as a sensitive and fairly specific marker of acute enterocyte injury (15, 16). In neonates with necrotising enterocolitis and children with intestinal ischaemia, serum I-FABP rises within hours and falls with clinical recovery (17, 18).

In the context of T1D, elevated I-FABP levels have been reported in both children and adults. A cross-sectional study in patients with type 2 diabetes showed that I-FABP levels increased with longer duration of hyperglycaemia and glucose variability, and were highest in those with retinopathy (19). In a paediatric cohort of children and adolescents with T1D, higher FABP2 concentrations were significantly linked to early kidney damage and subclinical vascular changes (carotid intima-media thickness), independent of glycaemic control (20). In adults with long-standing T1D, elevated serum I-FABP was associated with coronary artery stenosis after adjusting for conventional risk factors (21).

Importantly, children with T1D and co-existing coeliac disease showed a 50% reduction in I-FABP after starting a gluten-free diet, yet IFABP remained elevated in T1D patients without coeliac disease, suggesting that gluten-independent mechanisms, such as viral infections, gut dysbiosis, and glycaemic excursions, perpetuate enterocyte damage (22). Figure 1 illustrates how I-FABP release from injured enterocytes allows microbial products to enter the bloodstream, activating TLR4 on immune cells and driving the differentiation of autoreactive Th1/Th17 cells against beta cells.

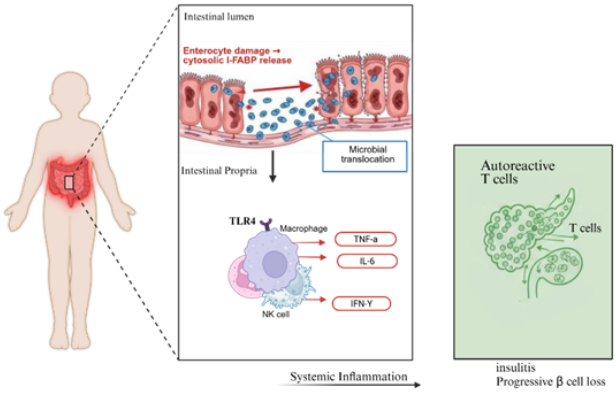


Figure 1 (conceptual): I-FABP as a distress signal linking gut injury to systemic inflammation in paediatric T1D

Platelet-activating factor, platelet signalling, and microvascular inflammation

Platelet-activating factor (PAF) is a potent phospholipid mediator first described in 1974 as a basophil-derived factor that causes platelet aggregation (23). Its structure – 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine – was elucidated in 1979 (24). PAF is produced by mast cells, monocytes, macrophages, platelets, eosinophils, endothelial cells, and neutrophils in response to inflammatory stimuli (25). It acts at very low concentrations (10^{-12} to 10^{-9} M) in an autocrine, juxtacrine, and paracrine manner (26).

Two main biosynthetic pathways exist (27)

Remodelling pathway (primary in inflammation)

Upon cell activation, cytosolic phospholipase A_2 ($cPLA_2$) hydrolyses alkyl-PC to produce lyso-PAF, which is then acetylated by lyso-PAF acetyltransferase (LPCAT) to form active PAF.

De novo pathway

Contributes to basal, physiological levels of PAF via a three-step process involving choline phosphotransferase.

PAF is rapidly degraded by PAF acetylhydrolases, which remove the acetyl group to generate inactive lyso-PAF (28). This short half-life tightly regulates PAF signalling.

At low concentrations, PAF participates in normal host defence, blood pressure regulation, and reproduction. However, excessive PAF causes increased vascular permeability, circulatory collapse, decreased cardiac output, and production of other inflammatory mediators (TNF-α, IL-1β, IL-6, eicosanoids), leading to leukocyte adhesion, chemotaxis, and tissue damage (28, 29, 30). In the setting of a "leaky gut", bacterial LPS translocate into the bloodstream, promoting chronic low-grade endotoxaemia that can amplify PAF production (31).

In diabetes, platelets are hyperactive, showing increased adhesion and thromboxane A_2 production (32). PAF further stimulates platelet activation, up-regulating P-selectin (CD62P) and facilitating platelet-leukocyte interactions within inflamed vessels. This process activates endothelial cells, up-regulating adhesion molecules such as ICAM-1 and promoting NF-κB-dependent transcription of TNF-α and MCP-1 (33, 34).

Özdemir and colleagues (2005) found significantly elevated serum PAF levels in children with T1D, with the highest levels in newly diagnosed patients, suggesting that PAF acts as an early inflammatory mediator in beta-cell destruction (35). Earlier work from 1985 demonstrated that platelets from T1D patients exhibit heightened sensitivity to PAF-induced aggregation compared to healthy controls, promoting a hypercoagulable state (36). Figure 2 summarises the PAF signalling cascade in diabetes.

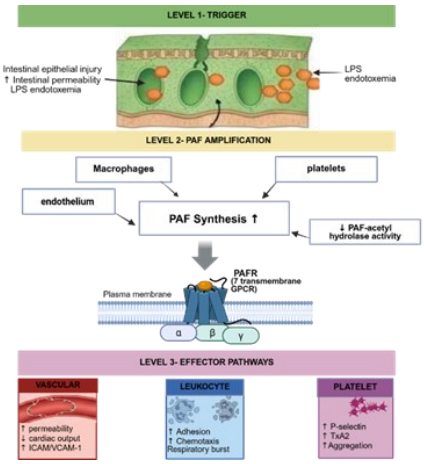


Figure 2 (conceptual): PAF signalling cascade in diabetes – gut-derived LPS triggers PAF overproduction, driving parallel vascular, leukocyte, and platelet activation pathways

Despite this evidence, paediatric-specific studies on PAF remain limited, and none have examined its relationship with I-FABP or miRNAs in the same cohort.

Circulating and tissue microRNAs in gut barrier dysfunction and immune activation

MicroRNAs (miRNAs) are small (≈20 nucleotides) non-coding RNA molecules that regulate gene expression post-transcriptionally by binding to target mRNAs, leading to translational repression or degradation (37). They play essential roles in epithelial barrier maintenance, oxidative stress responses, autophagy, and immunity (38). Dysregulated miRNAs are increasingly recognised as both biomarkers and functional mediators in T1D.

Serum miRNA profiles during preclinical and early disease stages

Several longitudinal studies have examined miRNA expression in children at risk for T1D. A 2022 study that followed 110 children from autoantibody positivity (Ab^+) through recent onset T1D to 2–5 years post-onset identified 69 differentially expressed miRNAs (DEMs) in serum compared to healthy controls; most changes were already detectable in the Ab^+ stage, before hyperglycaemia (39). In another study on high-risk children (those with multiple islet autoantibodies), researchers did not identify one miRNA that set the at-risk group apart from healthy kids, but they did see some miRNAs linked to glucose tolerance and autoantibody levels. In other words, these miRNAs reflect subtle metabolic and immune shifts (40). In TrialNet, among 150 autoantibody-positive versus 150 autoantibody-negative relatives, 93 serum miRNAs popped up; some of these gave extra clues about progression toward clinical T1D, beyond classic risk factors (41).

Associations with inflammation, the gut barrier, and platelet/vascular pathways

Across kids and mixed-age groups, miRNAs like miR-21, miR-29, miR-146a, miR-155, and miR-210 keep showing up with T-cell activation, cytokine release, and NF-κB/STAT signalling; basically, they echo systemic inflammation that starts in the gut lining and spreads to the immune system (42, 43, 44). There are miRNAs linked to endothelial and platelet function, especially miR-126 and miR-223, and these control blood vessel repair, how white cells stick, and how platelets behave. In kids with T1D, off-balance levels point to early action in the endothelium and platelets, not just what's happening to beta cells (45, 46).

miRNAs that control the gut barrier

A bunch of miRNAs go right after tight junction proteins and tweak gut permeability. Table 1 lays out the main examples.

Table 1: Selected miRNAs that regulate intestinal barrier integrity

miRNA	Principal validated targets	Functional consequence	Key reference
miR-21	Occludin, RhoB	TJ disassembly, increased paracellular flux	(47)
miR-122a	Occludin 3′-UTR	mRNA degradation, increased permeability	(47)
miR-155	RhoA, SHIP-1	Decreases ZO-1 and claudin-1; sensitises barrier to TNF-α	(47)
miR-146a, miR-323b-5p	TLR4, IRAK1	Reduces IL-6/IL-8, increases TER, ZO-1/occludin	(48)
miR-595	NCAM-1, FGFR2	Maintains claudin-4, promotes epithelial repair	(49)
miR-197-3p	Unknown protective axis	Preserves occludin in coeliac biopsies; elevated in active disease	(49)

TER = transepithelial electrical resistance; TJ = tight junction

Even though there are not many direct studies linking serum miRNAs to intestinal barrier markers like I-FABP in kids with type 1 diabetes, research in the gut shows that these same miRNAs, miR-21, miR-29, and miR-223, actually regulate tight junction proteins and intestinal inflammation. So, it's pretty likely that these "common" miRNAs connect gut permeability, chronic inflammation in the body, and the autoimmune attack on beta cells.

An integrated gut-immune-pancreatic axis model in children

Here's how all the pieces fit together (see Figure 3)

Early damage to the intestinal barrier

Genetics set the stage, and then environmental factors like diet, viruses, or gut microbiome imbalance trigger a problem. Tight junctions between gut cells get disrupted, and enterocytes get hurt. When that happens, I-FABP leaks into the bloodstream, which makes it a sensitive marker of early damage.

Increased gut permeability

Once the barrier's down, bacterial stuff like LPS sneaks into the portal and systemic blood (endotoxemia). This kicks off ongoing low-grade inflammation.

PAF amplifies inflammation

LPS and inflammatory cytokines activate macrophages, neutrophils, and platelets, which then crank out PAF through the remodelling pathway. PAF makes blood vessels leakier, draws in more immune cells, and keeps platelets fired up, triggering an inflammatory loop that keeps feeding itself.

miRNA imbalance

The gut's inflamed lining and immune cells start changing their miRNA patterns (for example, miR-21 and miR-155 go up, miR-146a drops). These miRNAs get released into the blood, where they (a) further break down tight junctions, (b) push T cells toward a pro-inflammatory profile (Th1/Th17), and (c) mess with how platelets and endothelial cells act. At the same time, some of these circulating miRNAs try to rein in inflammation but usually lose the fight in kids who are genetically vulnerable.

Beta cell autoimmunity

After all that, the immune system starts showing microbial antigens, cranking out pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ), and regulatory T cells lose their grip. Autoreactive T cells expand and head for the pancreas. Islet-specific autoantibodies pop up, and the beta cell population keeps shrinking. Kids start showing clinical T1D symptoms after about 70–90% of beta cells are gone.

This model says the step from having autoantibodies but no symptoms to full-blown T1D depends. at least partly, on how severe and how long the gut barrier stays messed up, and what that does to inflammation across the body. It also highlights early targets for intervention: keep tight junctions intact, block LPS or PAF, or fix the miRNA patterns.

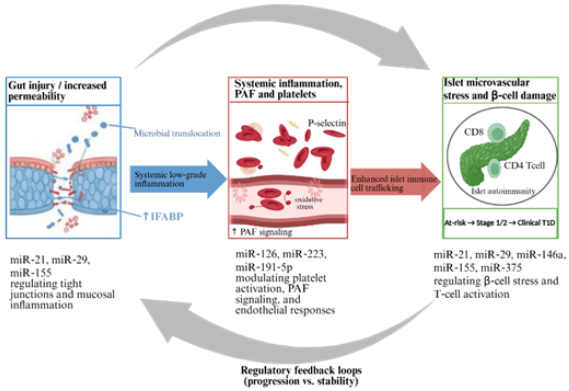


Figure 3 (conceptual): Integrated mechanistic model of the gut-immune-pancreatic axis in children with T1D. I-FABP, PAF, and miRNAs act across the gut, blood, and islets to modulate disease progression

Importance and relevance

Thinking of T1D as a disease that's not just about the pancreas, but also the gut and blood vessels, opens the door for better ways to figure out who's at risk and when to step in early. Let's say you measured I-FABP and checked a panel of miRNAs in kids who already test positive for islet autoantibodies. That could help predict who'll move on to clinical T1D. On top of that, things like high-fibre diets (to boost short-chain fatty acids), probiotics (to strengthen the gut lining), or drugs that block PAF might slow or even prevent the destruction of beta cells. But, just to be clear, those strategies are still experimental.

Limitations and future directions

Right now, the evidence is patchy; sample sizes are small, designs are mostly cross-sectional, and there's a real shortage of good paediatric-focused, long-term studies. Most of what we know comes from adults or animal models. Plus, we still haven't seen studies that look at I-FABP, PAF, and miRNAs in the same group of kids at the same time. There's a real need for solid, forward-looking studies in African and other underrepresented populations, since genetic backgrounds and environmental exposures there don't always match what you find in Europe or North America. Future research should pull everything together: barrier markers, microbiome profiles, PAF and miRNA measurements, and clinical outcomes.

All in all, the gut-immune-pancreas axis is a promising way to look at paediatric T1D. If we can prove that I-FABP, PAF, and miRNAs work as a practical biomarker panel, it could change the game for early T1D diagnosis and give us new windows for treatment before the disease takes hold.

Conclusion

In this review, we pulled together the science on three groups of biomarkers, I-FABP, PAF, and miRNAs, and slotted them into an overall gut-immune-pancreas axis model for T1D in kids. The main points boil down to this:

High I-FABP signals ongoing gut lining damage and increased permeability, and these changes often show up before T1D hits.

PAF sits at the centre of the inflammation process, connecting gut endotoxemia to platelet activity, endothelial dysfunction, and small blood vessel complications.
miRNAs like miR-21, miR-146a, miR-155, and miR-223 help regulate gut tight junctions, immune cell balance, and platelet behaviour. This network might determine when a child at risk actually develops clinical disease.

List of Abbreviations

Ab$^+$: Autoantibody positive
$cPLA_2$: Cytosolic phospholipase A_2
DEM: Differentially expressed miRNA
DKA: Diabetic ketoacidosis
GADA: Glutamic acid decarboxylase antibody
HLA: Human leukocyte antigen
IAA: Insulin autoantibody
IA 2: Insulinoma-associated antigen 2
ICA: Islet cell cytoplasmic antibody
ICAM 1: Intercellular adhesion molecule 1
IFN γ: Interferon gamma
IL: Interleukin
IFABP: Intestinal fatty acid binding protein (FABP2)
LPS: Lipopolysaccharide
MCP 1: Monocyte chemoattractant protein 1
miRNA: MicroRNA
NF κB: Nuclear factor kappa light chain enhancer of activated B cells
PAF: Platelet-activating factor
SCFA: Short-chain fatty acid
T1D: Type 1 diabetes
TER: Transepithelial electrical resistance
TJ: Tight junction
TLR4: Toll-like receptor 4
TNF α: Tumour necrosis factor alpha
Treg: Regulatory T cell
ZO 1: Zonula occludens 1

Declaration

Ethics approval and consent to participate
Not applicable. This is a narrative review; no primary data from human participants were collected or reported.

Consent for publication
All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials
All data analysed in this review are from previously published studies as cited in the reference list. No new datasets were generated.

Competing interests
The authors declare that they have no competing interests.

Funding
This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions
AAZ and ASA: Conceptualisation, Writing – original draft preparation
AAZ, ASA and MAJ: Methodology, Writing – review and editing
MAJ: Visualisation
AAZ: Project administration
All authors have read and agreed to the published version of the manuscript.

Acknowledgments
The authors thank the staff of the Babcock University Medical Journal editorial office for guidance on the journal's formatting requirements. Figures were conceptualised by the authors and created with https://biorender.com/ under a paid academic licence.

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