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Gestational Diabetes as an inter-generational cardiometabolic risk factor: spotlight on emerging exerkines

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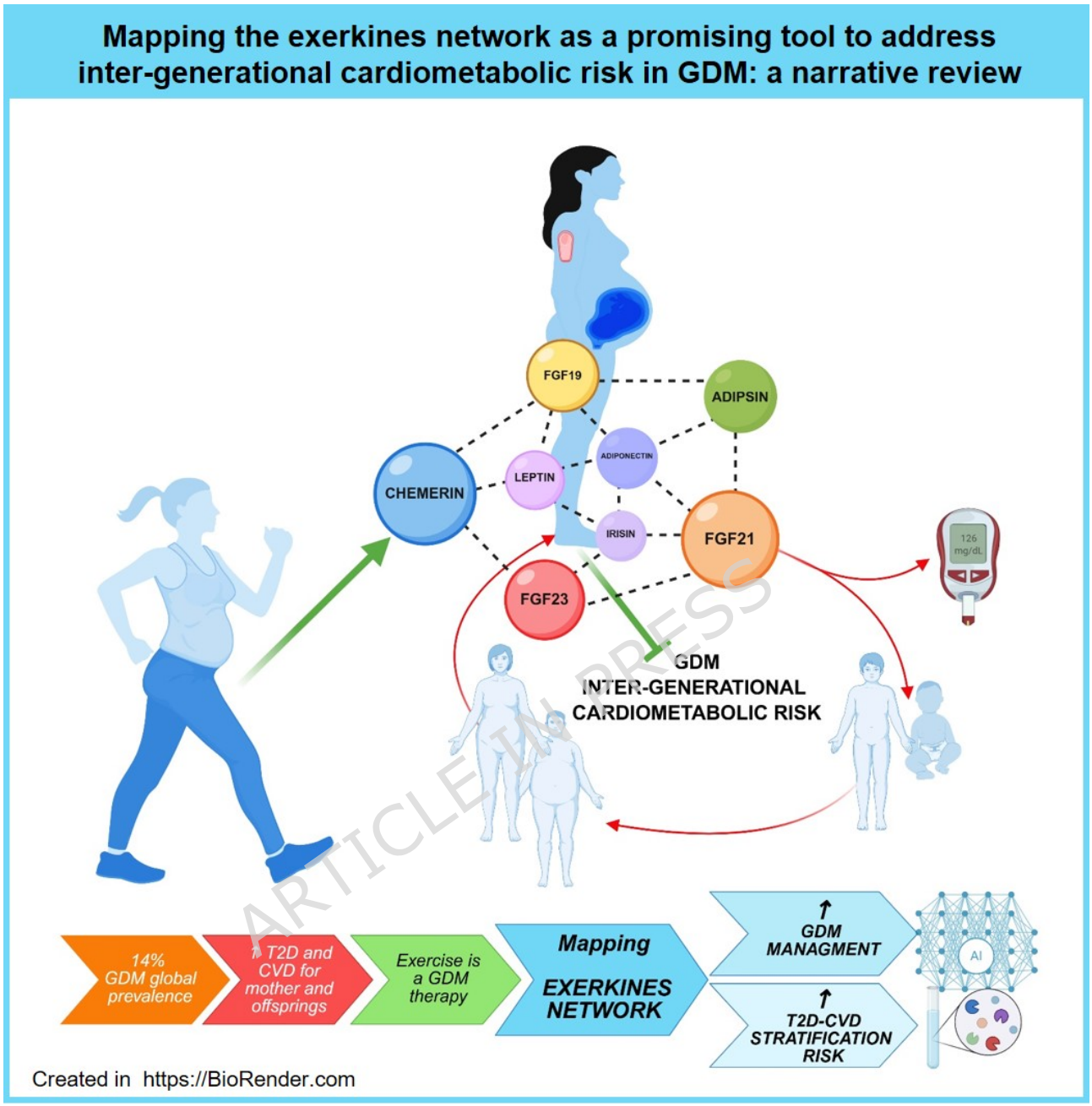
Graphical abstract



Research Insights

What is currently known about this topic? The mediators of exercise-induced benefit in GDM, a condition linked to intergenerational cardiometabolic risk, remain only partially understood
What is the key research question?

Which exerkines involved in GDM influence maternal and offspring cardiometabolic outcomes?
What is new? Emerging exerkines, including chemerin, FGF19 family members, and adipsin, may contribuite to GDM pathophysiology and cardiometabolic regulation
How might this study influence clinical practice? Characterising the exerkine network may help optimise GDM management and improve cardiometabolic risk stratification

Keywords: adipokines, enterokines, chemerin, FGF21, FGF19, FGF23, adipsin, GDM biomarkers, cardiovascular disease.

Abstract

Gestational diabetes mellitus (GDM) is an increasingly prevalent global health condition, driven by rising maternal age and the obesogenic environment, currently affecting approximately 14% of pregnancies worldwide. GDM is associated with adverse perinatal outcomes as well as a substantial increase in long-term cardiometabolic risk.

Women with a history of GDM exhibit a markedly elevated risk of developing type 2 diabetes (T2D) within the first decade postpartum, together with an approximately twofold higher risk of major cardiovascular events. Importantly, offspring of mothers with GDM are also predisposed to obesity and T2D later in life, underscoring the role of GDM as a major intergenerational determinant of cardiometabolic disease.

Physical activity is recommended as an effective non-pharmacological strategy for the prevention and management of GDM; however, the molecular mechanisms underlying its benefits remain only partially understood. Exerkines, bioactive molecules modulated by exercise, have emerged as important regulators of systemic metabolic and cardiovascular adaptations.

In addition to the well-characterised exerkines such as leptin, adiponectin, and irisin, emerging evidence supports the relevance of additional mediators, including chemerin, members of the FGF19 subfamily, and adipsin, as contributors to the pathophysiology of GDM and cardiovascular risk. This narrative review summarises the current evidence on these emerging exerkines, focusing on their biological mechanisms and clinical relevance in GDM. A deeper understanding of the exerkine network may provide novel insights into the interplay between exercise, metabolic regulation, and pregnancy, ultimately supporting improved GDM management and long-term cardiometabolic risk stratification across generations.

Introduction

Gestational diabetes mellitus (GDM), one of the most common complications of pregnancy, is defined as ‘glucose intolerance first recognized during pregnancy”. The utilisation of the term “recognize” in lieu of “onset” reflects the current diabesity pandemic, as GDM often reveals previously undiagnosed hyperglycaemia or type II diabetes (T2D), which is often concomitant with obesity. The obesogenic environment substantially contributes to the rising global prevalence of GDM, which currently affects approximately 14% of pregnancies worldwide (one in six live births) [1].

GDM not only increases the risk of adverse pregnancy outcomes, including preeclampsia (PE), preterm birth and macrosomia, but also significantly elevates long-term cardiometabolic risk. Although, glucose levels typically normalize after delivery, women with a history of GDM remain at markedly increased risk of developing T2D within the first decade postpartum [2]. Moreover, a recent meta-analysis by Kramer CK et al. showed that women with prior GDM have an approximately twofold higher risk of major cardiovascular events, independently of subsequent T2D development, with this increased risk becoming apparent within 10 years after delivery [3].

According to Barker’s Hypothesis and the Developmental Origins of Health and Disease (DOHaD) framework, the intrauterine environment plays a critical role

in shaping long-term metabolic health. Children born to mothers with GDM are at increased risk of developing obesity, insulin resistance, and T2D later in life [4]. Maternal hyperglycaemia has also been associated with alterations in foetal adiposity and hypothalamic development, potentially affecting appetite regulation and long-term metabolic programming [5]. These changes may contribute to an increased lifetime risk of cardiovascular diseases (CVD) in the offspring. Consistently, a large Danish population-based cohort study (including live births in Denmark between 1977-2016) reported higher rates of early-onset CVD among children born to mothers with diabetes [4].

For these reasons, GDM is increasingly recognized as an intergenerational cardiometabolic condition affecting both maternal and offspring health [6, 7]. Identifying individuals at risk and implementing effective preventive and therapeutic strategies are therefore essential to reducing the growing global burden of cardiometabolic disease.

Current management of GDM relies primarily on lifestyle interventions and, when necessary, pharmacological treatment, mainly insulin therapy [8]. Dietary intervention remains a cornerstone of GDM management; however, growing evidence also highlights the important role of physical exercise, not only in the prevention of GDM but also in improving glycaemic control and cardiometabolic outcomes during pregnancy [9]. Accordingly, the American Diabetes Association recommends that women with GDM engage in approximately 30 minutes of moderate physical activity on most days of the week, including aerobic exercise and resistance training, and walking after meals [10].

Despite these well-established clinical benefits, the cellular and molecular mechanisms through which exercise exerts its cardiometabolic effects during pregnancy remain only partially understood. Clarifying these pathways may help to support the development of more personalized exercise-based strategies, with the dual aim of improving maternal metabolic health and mitigating adverse cardiometabolic programming in the offspring.

In recent years, increasing attention has focused on exerkines, exercise-induced bioactive molecules that mediate part of the systemic adaptations to physical activity [11]. Secreted by multiple tissues, including skeletal muscle, adipose tissue, liver and the heart, these molecules may play a key role in the crosstalk between exercise and metabolic and cardiovascular regulation [12]. Several exerkines, including leptin, adiponectin, and irisin have already been extensively studied in the context of pregnancy and GDM [13-16], where they appear to participate in the regulation of insulin sensitivity, energy metabolism, and cardiometabolic adaptation. However, emerging evidence suggests that additional exercise-responsive molecules may also contribute to the complex pathophysiology of GDM and its long-term consequences.

Growing attention has therefore been directed toward novel exerkines involved, including chemerin, members of the fibroblast growth factor 19 subfamily (FGF19s), and adipsin. Although evidence directly linking these molecules to exercise in GDM is still limited, they are increasingly recognized as potential mediators of cardiometabolic regulation and may offer new mechanistic insights into the interplay between physical activity, metabolic homeostasis, and cardiovascular risk during pregnancy. In this narrative review, we focus on these emerging exerkines and discuss their potential role in the pathophysiology of GDM, their modulation of exercise, and their possible implications for intergenerational cardiometabolic risk.

Literature search strategy

Relevant literature was primarily identified through the PubMed, Scopus, and Web of Science databases using keywords related to gestational diabetes mellitus, exercise, exerkines, and cardiometabolic health. Inclusion criteria comprised original studies and review articles written in English and published in peer-reviewed journals. Articles were selected based on their relevance to the scope of the review, with particular attention to experimental and clinical evidence on emerging exerkines and, a primary focus on studies published in recent years (2021–2026).

Chemerin: an emerging exerkine at the crossroads of GDM and cardiometabolic health

Among the emerging exekines potentially involved in the pathophysiology of GDM, chemerin has gained increasing attention for its multifaceted role in cardiometabolic health and placental function [17].

Chemerin: cellular mechanisms of action

The term “chemerin” was introduced in 2003, replacing the original designation tazarotene-induced gene 2, when the previously orphan G protein-coupled receptor ChemR23 was identified as receptor of a protein first described in 1997 in psoriatic skin lesions [18].

As illustrated in Figure 1, chemerin, predominantly secreted by white adipose tissue (WAT), is synthesised as an inactive precursor (preprochemerin) that undergoes post-translational processing and proteolytic cleavage, generating several bioactive isoforms [19-21] that interact with three distinct receptors [22].

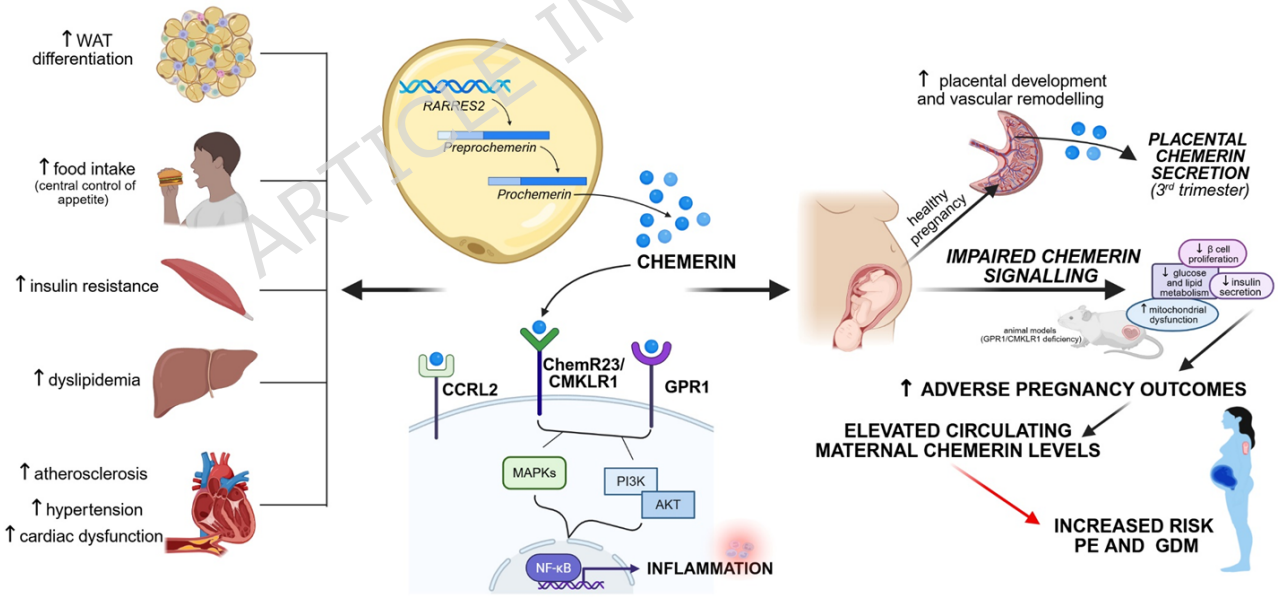


Figure 1. Chemerin signalling in cardiometabolic regulation and GDM
Chemerin is an adipose tissue–derived signalling molecule that primarily acts through CMKLR1 (ChemR23), with additional binding to GPR1 and CCRL2, activating downstream MAPK, PI3K/AKT, and NF-κB pathways. These signalling cascades underlie its effects on adipocyte differentiation, insulin sensitivity, lipid metabolism, and vascular function. In addition, emerging evidence indicates that chemerin contributes to the regulation of energy balance and food intake. During pregnancy, placental-derived chemerin supports vascular remodelling, whereas dysregulated signalling and elevated circulating levels are associated with adverse outcomes, including GDM and PE.
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Among these receptors, ChemR23, also known as chemerin-like receptor 1 (CMKLR1) is the most extensively studied. It is widely expressed in immune cells and is also present in the liver, skeletal muscle, cardiac tissue and placenta. Activation of the chemerin/CMLR1 axis mediates mitogenic responses mainly through mitogen-activated protein kinase (MAPK)/Extracellular signal-Regulated Kinase (ERK) signalling and promotes pro-inflammatory pathways regulated by transcription nuclear factor-κB (NF-κB) [22]. The physiological roles of the other chemerin receptors, G protein-coupled receptor 1 (GPR1) and CC motif chemokine receptor-like 2 (CCRL2), remain less clearly defined. GPR1 appears to share signalling pathways with CMKLR1, whereas CCRL2 functions as a non-signalling receptor that facilitates chemerin interaction with active receptors [23, 24].

Chemerin: role in cardiometabolic health

Both animal and human studies have established a central role for chemerin in the modulation of inflammatory processes [25]. Elevated circulating chemerin levels have been reported in several chronic inflammatory and immune-mediated diseases, including rheumatoid arthritis, chronic obstructive pulmonary disease and various cancers [26]. Recent studies have highlighted a strong association between chemerin and key components of cardiometabolic risk [27]. Elevated chemerin levels are linked to visceral adiposity and low-grade systemic inflammation [28, 29]. Accumulating evidence suggests that chemerin promotes white adipose-tissue, remodelling by enhancing preadipocyte differentiation and angiogenesis [30-32].

Emerging evidence also indicates that chemerin may contribute to the central regulation of appetite. In animal models, blockade of hypothalamic CMKLR1, through pharmacological or genetic approaches, markedly reduces weight gain [33]. Chemerin may influence hypothalamic remodelling and feeding behaviour by acting on tanycytes, specialised glial cells involved in nutrient sensing and neuropeptide regulation [34].

In peripheral tissues, chemerin has also been implicated in skeletal muscle insulin resistance, where CMKLR1 signalling interferes with insulin-stimulated glucose uptake and metabolic flexibility [35].

Higher circulating chemerin levels have been associated with increased blood pressure, suggesting a potential vasoconstrictor role [36]. Chemerin is also linked to dyslipidaemia and other cardiometabolic alterations that favour vascular dysfunction and atherosclerosis [37]. Mechanistically, activation of the chemerin/CMKLR1 axis promotes endothelial progenitor cell adhesion, leukocyte recruitment and vascular remodelling, partly through impaired endothelial nitric oxide synthase (eNOS) activity [38, 39].

Chemerin may also exert deleterious effects on cardiac function and electrophysiology, particularly by exacerbating diabetes-induced cardiac damage [40, 41].

Consistently, a recent meta-analysis reported significantly higher circulating chemerin levels in patients with acute coronary syndrome and T2D compared with individuals without diabetes [42].

Chemerin: pathological role in GDM

Given these findings, the role of chemerin in pregnancy complications has attracted increasing attention.

Several studies have highlighted a physiological role for chemerin in placental development [43]. In murine models, CMKLR1 deficiency has been associated with adverse pregnancy outcomes, likely due to impaired placental development, vascular remodelling, and alterations in chemerin-related lipid metabolism during early pregnancy [44-46]. Notably, dysregulation of the chemerin/CMKLR1 axis, characterised by low circulating chemerin levels, has been associated with an increased risk of miscarriage during the first trimester [47].

After its formation, the placenta itself becomes an important source of chemerin, and circulating levels fluctuate throughout pregnancy, typically peaking in the third trimester [48].

A growing body of evidence supports the involvement of chemerin in the pathophysiology of GDM [49, 50]. Experimental studies indicate that chemerin signalling influences glucose metabolism during pregnancy. For example, GPR1 knockout in pregnant mice worsens glucose intolerance, impairs lipid metabolism, and reduces β-cell proliferation and insulin secretion [51]. Moreover, recent studies have suggested a link between elevated chemerin levels and mitochondrial dysfunction in placental cells [52].

In a GDM mouse model, dysfunction of the chemerin-CMKLR1 axis has also been associated with reduced neuronal numbers and cognitive impairment in the offspring [61], reinforcing the concept that the intrauterine environment plays a crucial role in shaping long-term offspring health.

These experimental findings are supported by clinical evidence [54]. Recent meta-analyses have confirmed that circulating chemerin levels are significantly elevated in women with GDM [55]. Importantly, these analyses help clarify inconsistencies observed in earlier smaller studies, which did not consistently detect differences in chemerin levels between GDM and normoglycaemic pregnancies. Such discrepancies likely reflect heterogeneity in study design, including differences in the gestational timing of adipokine assessment and underlying metabolic risk (Table 1).

In addition, increasing evidence suggests that chemerin contributes to inflammation and aberrant placental vascular remodelling, two key hallmarks of PE, and circulating chemerin levels are consistently elevated in women with PE [56].

Collectively, these findings suggest that chemerin may represent a promising biomarker and potential therapeutic target for pregnancy-related metabolic complications, particularly GDM.

Chemerin: response to exercise

Exercise is one of the most important physiological modulators of circulating chemerin levels. Several studies have demonstrated that aerobic, resistance and combined training programmes significantly reduce circulating chemerin concentrations in individuals with metabolic diseases [57].

Experimental studies further suggest that the reduction in chemerin may represent one of the mechanisms through which exercise exerts its metabolic benefits. Zhang Q et al. investigated this hypothesis using wild-type and systemic chemerin knockout mice fed a high-fat diet and subjected to a moderate-intensity aerobic programme for eight weeks [58]. Their findings showed that the reduction in chemerin levels was essential for exercise-induced glucagon-like peptide-1 (GLP-1) secretion and improved pancreatic □-cell function.

Similarly, Lin X et al. reported that reduced chemerin levels enhanced exercise-induced improvements of glucose and lipid metabolism and attenuated fatty liver in diabetic mice through mechanisms involving peroxisome proliferator-activated receptor γ (PPARγ) signalling [69].

In addition, Ahmadabadi F et al. demonstrated that exercise-induced reductions in chemerin secretion from the liver and adipose tissue, together with increased irisin levels, contributed to attenuation of cardiovascular risk in rats with metabolic syndrome [60].

Taken together, these findings support the hypothesis that modulation of chemerin signalling may represent one of the molecular pathways through which exercise improves cardiometabolic health. In the context of GDM, this raises the possibility that part of the preventive and therapeutic effects of physical activity may be mediated through changes in circulating chemerin levels.

Chemerin: key gaps and perspectives

From a mechanistic perspective, further studies are needed to clarify the cellular pathways through which chemerin influences metabolic and cardiovascular adaptations during pregnancy, including the potential role of distinct chemerin isoforms and the signalling cascades activated by its different receptors.

From a clinical standpoint, larger longitudinal studies are warranted to consolidate emerging evidence supporting chemerin as a biomarker of GDM and to identify the most informative diagnostic window during pregnancy.

In this context, given the growing interest in exercise-based interventions for GDM prevention and management, investigating how structured physical activity programmes modulate circulating chemerin levels in women with GDM or at high risk of GDM represents an important and currently underexplored research avenue.

FGF21: the stress-responsive exerkine as new therapeutic opportunities for GDM

The endocrine subfamily FGF19s, which includes FGF21, FGF19, and FGF23, has attracted increasing attention for its multifaceted roles in metabolism, cardiovascular function, and foetal development. Among these endocrine FGFs, FGF21, first identified in 2000, is the most extensively studied member of the family [61].

FGF21: cellular mechanisms of action

FGF21 is predominantly expressed in the liver, although lower levels are also detected in WAT and brown adipose tissue (BAT), pancreas, skeletal muscle, and heart.

Inagaki T et al. identified peroxisome proliferator-activated receptor-α (PPARα) as a major transcriptional regulator of FGF21, capable of binding the FGF21 promoter and increasing its expression during fasting [63].

As illustrated in Figure 2, hepatic FGF21 expression is strongly induced by prolonged fasting and several forms of nutritional stress, including ketogenic diets, amino acid deprivation, and excessive sugar intake, particularly fructose. In addition to PPARα, other transcriptional regulators of FGF21 include PPARɣ and activating transcription factor 4 (ATF4) and carbohydrate response element-binding protein (ChREBP), a key regulator of carbohydrate-responsive gene expression [64, 65].

Similar to other members of the FGF19 subfamily, FGF21 requires co-receptors to exert its endocrine effects due to its low affinity for transmembrane tyrosine kinase FGF receptors (FGFRs) [68]. Specifically, FGF21 interacts with the cofactor β-klotho (KLB) and primarily binds FGFR1c [66]. Downstream, the FGF21/KLB complex primarily activates several signalling pathways involved

in energy regulation and antioxidant response, including MAPK pathway, AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) pathway [67, 68]. Additional signalling networks, such as PI3K-dependent pathways, remain incompletely characterised. This stress-responsive endocrine signalling supports the role of FGF21 as a key integrator of nutrient availability, energy balance, and systemic metabolic adaptation.

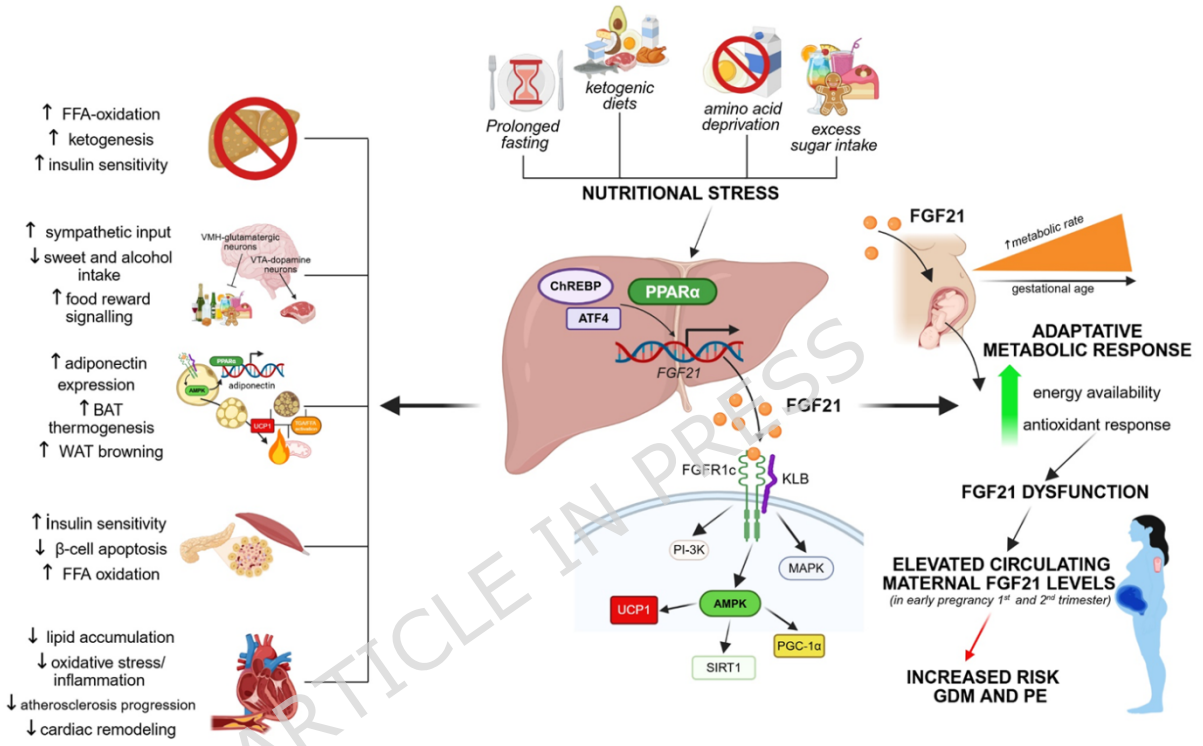

Figure 2. FGF21 as a stress-responsive exerkine in metabolic adaptation and GDM
FGF21 is a liver-derived endocrine factor induced by nutritional stress (e.g. fasting, ketogenic diet, and macronutrient imbalance) through transcriptional regulators including PPARα, ATF4, and ChREBP. Acting via the FGFR1c/β-klotho complex, FGF21 activates downstream pathways, including AMPK signalling, promoting fatty acid oxidation, thermogenesis, insulin sensitivity, and antioxidant responses. Notably, FGF21 stimulates adiponectin secretion from adipose tissue, which acts as a key downstream mediator amplifying its systemic metabolic effects. During pregnancy, FGF21 contributes to adaptive metabolic responses, while elevated circulating levels, particularly in early gestation, are associated with increased risk of GDM and PE.
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FGF21: role in cardiometabolic health

In the liver, FGF21 acts as a hepatoprotective factor against steatosis and liver injury by enhancing the transcription of genes involved in mitochondrial biogenesis and ß-oxidation, including peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1α) [69]. Consistently, FGF21-deficient

mice fed a methionine- and choline-deficient diet develop severe steatosis associated with an enhanced inflammatory state [70].

FGF21 also influences food intake and central metabolic regulation. It modulates glutamatergic neuronal activity in the ventromedial hypothalamus (VMH), suppressing sweet consumption and alcohol intake [71, 72], and acts on dopamine neurons in the ventral tegmental area (VTA), enhancing the rewarding value of protein-containing foods and promoting their consumption [73, 74]. In line with this, neuronal FGF21 or KLB knockout models display a blunted adaptive response to protein restriction, supporting a role for FGF21 signalling in systemic energy balance and metabolic adaptation, including increased sympathetic input to the liver and suppression of hepatic de novo lipogenesis [75, 76].

FGF21 further emerges as an important regulator of adipose tissue endocrine function, thermogenesis, and tissue remodelling. Both preclinical and clinical studies indicate that acute and chronic FGF21 stimulation increases adiponectin expression and secretion, at least partly through PPARɣ-dependent mechanisms. Adiponectin, acting through AdipoR1 and AdipoR2, mediates many of the downstream systemic effects of FGF21, including improved insulin sensitivity and reduced inflammation and oxidative stress. Consistently, adiponectin deficiency markedly attenuates the insulin-sensitising effects of FGF21, highlighting the functional relevance of the FGF/adiponectin axis [77, 78].

FGF21 also enhances Uncoupling Protein 1 (UCP1) expression in BAT, stimulating mitochondrial biogenesis and thermogenesis [79-81]. Studies in UCP1-deficient mice suggest that FGF21 may additionally promote energy dissipation through triacylglycerol/free fatty acid cycling independently of UCP1 [81]. In WAT, FGF21 promotes browning by PPARγ activation [82].

In addition, FGF21 exerts protective effects on pancreatic ß-cells and skeletal muscle, acting as an insulin-sensitising factor and improving glucose metabolism [83-85].

A growing body of evidence also indicates that FGF21 contributes to cardiovascular protection [86, 87]. In experimental models, FGF21 deficiency leads to eccentric cardiac hypertrophy, whereas restoration of FGF21 signalling alleviates hypertrophy and fibrosis [88-90].

Clinically, elevated circulating FGF21 levels are observed not only in obesity, metabolic dysfunction–associated steatotic liver disease (MASLD), and T2D, but also in individuals with cardiovascular disease [91, 92]. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, higher FGF21 levels were associated with an increased risk of cardiovascular events [93].

Overall, elevated circulating FGF21 appears to reflect an adaptive metabolic stress response. However, as observed for insulin and leptin, chronic metabolic diseases may also be associated with a state of FGF21 resistance. This condition is characterised by reduced expression of the FGFR1c/KBL receptor complex in target tissues and impaired downstream signalling [94, 95].

Enhancing FGF21 signalling has therefore become an important therapeutic goal in cardiometabolic medicine, and the clinical development of FGF21 analogues and mimetics highlights the translational potential of this hepatokine. Across clinical trials, FGF21-based therapies have shown consistent improvements in lipid metabolism, particularly triglyceride lowering, whereas effects on body weight and glycaemic control appear more variable, with some early analogues failing to meet weight-loss endpoints (e.g., LY2405319) [96,97].

More recently, new FGF21-based agents have shown encouraging metabolic effects. Efruxifermin (EFX), a long-acting FGF21 fusion protein targeting both hepatic and adipose tissues, improves metabolic parameters and stimulates adiponectin secretion [98]. Similarly, MK-3655, a monoclonal antibody activating the FGFR1c/KBL complex, enhances glucose disposal in individuals with insulin resistance [96].

FGF21: pathological role in GDM

In pregnancy, FGF21 has emerged as a candidate biomarker for GDM [99].

Several clinical studies have reported elevated circulating FGF21 levels in women with GDM, often in association with BMI and leptin concentrations [100,101] (Table 1). Importantly, in a nested case-control study, elevated FGF21 concentrations were already detectable at 14 to 21 gestational weeks in women who were later diagnosed with GDM at 24-28 gestational weeks, suggesting a potential predictive role for this hepatokine [102]. Subsequent meta-analyses further supported these observations, indicating that higher FGF21 levels may represent a biomarker not only of GDM but also of PE [103, 104].

Mechanistically, FGF21 may be involved in the adaptive response to hyperglycaemia-induced oxidative stress. In endothelial cellular models, Sun C et al. showed that L-cystine induced an FGF21-mediated antioxidative response characterised by nuclear factor erythroid 2-related factor 2 (Nrf2) translocation and upregulation of detoxing genes [105]. In agreement with these findings, clinical data demonstrated a positive correlation between circulating L-cystine and FGF21 levels in women affected by GDM [105]. Moreover, during pregnancy, FGF21 knockout and adipocyte-specific KLB mutant mice exhibited exacerbated inflammatory responses, whereas recombinant FGF21 administration attenuated inflammation [106].

Emerging evidence also suggests that dysregulation of FGF21 signalling may contribute to the intergenerational transmission of cardiometabolic risk. A study from the Danish National Birth Cohort reported altered circulating FGF21 levels together with reduced adiponectin concentrations in children and adolescents born to mothers with GDM, supporting the hypothesis that disruption of the FGF21/adiponectin axis may contribute to long-term offspring vulnerability [107].

Taken together, these findings suggest that in GDM condition, FGF21 acts as a stress-responsive metabolic signal and may represent both a biomarker of disease and a potential therapeutic target [108].

FGF21: response to exercise

Exercise is one of the most important physiological modulators of FGF21 signalling [109]. Experimental evidence suggests that exercise may improve metabolic health, at least in part, by restoring FGF21 sensitivity. In murine adipose tissue, Geng L. et al. showed that exercise reversed obesity-induced FGF21 resistance by upregulating FGFR1 and KLB through PPARγ signalling. Notably, FGF21 knockout or KLB-deficient mice failed to show exercise-induced improvements in glycaemic control and lipid metabolism, indicating that intact FGF21 signalling is a key mediator of exercise benefits [110].

Similarly, both high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) alleviated diabetes-induced cardiac injury in mice while improving the FGF21/KLB axis [111].

Human studies have confirmed this interaction between exercise and FGF21. Meta-analyses indicated that acute exercise increases circulating FGF21 levels, typically peaking about one hour after exercise, whereas chronic exercise induces adaptations that depend on training modality and metabolic status [112]. In particular, aerobic exercise appears to significantly increase FGF21 levels, especially in young and normal weight subjects [113]. By contrast, chronic aerobic training in individuals with overweight or obesity has been associated with reduced circulating FGF21 levels together with increased FGFR and KBL expression, suggesting improved FGF21 sensitivity [114]. Similarly, resistance training has been reported to reduce circulating FGF21 levels in elderly men with and without T2D, further supporting the hypothesis that chronic exercise may counteract FGF21 resistance [115].

Importantly, initial evidence is also emerging in pregnancy. In women with GDM, second-trimester circulating FGF21 levels were higher in sedentary subjects than in those treated with diet and exercise, while placental analysis at delivery showed upregulation of both Nrf2 and FGF21 following lifestyle intervention, suggesting improved antioxidant capacity [105]. In addition, maternal exercise in pregnant spontaneously hypertensive rats restored FGF21 signalling in offspring vessels through SIRT1 activation, normalising FGF21 expression and increasing FGFR1 levels [116].

These findings suggest that maternal exercise may modulate the FGF21 pathway in both mothers and offspring, supporting the concept that exercise acts as a physiological modulator of the FGF21 axis, potentially counteracting metabolic stress and restoring FGF21 sensitivity.

FGF21: key gaps and perspectives

Despite the extensive evidence supporting the metabolic and cardioprotective functions of FGF21, several aspects of its biology remain incompletely understood. In particular, the mechanisms underlying the development of FGF21 resistance in chronic metabolic diseases require further clarification, as this condition may limit the therapeutic potential of FGF21-based interventions.

Another aspect that warrants further investigation is the potential influence of sex and hormonal status on FGF21 signalling. Emerging evidence suggests a degree of sexual dimorphism in circulating FGF21 levels and responsiveness [117]. Both animal and clinical studies frequently report higher circulating FGF21 and adiponectin concentrations in females compared with males. However, preclinical studies indicate that treatment with FGF21 analogues or mimetics generally produces beneficial metabolic effects in both sexes but may exert stronger effects in males, particularly with regard to fat loss and insulin regulation, whereas females may display distinct or attenuated responses.

From a translational perspective, future studies should further investigate the role of FGF21 as a biomarker and therapeutic target in GDM and clarify how structured exercise interventions during pregnancy may modulate FGF21 signalling and metabolic adaptation.

FGF19: a fascinating emerging enterokine in GDM

Among the endocrine fibroblast growth factors, FGF19 represents a unique enterokine linking intestinal metabolism with systemic energy homeostasis. As a hormone primarily regulated by bile acid signalling, FGF19 has attracted growing interest as a mediator of gut-liver metabolic communication.

Emerging evidence suggests that, similarly to FGF21, FGF19 may also contribute to the pathophysiology of GDM [118].

FGF19: cellular mechanisms of action

Human FGF19 and its rodent orthologue, FGF15, were first identified in 1999 and are primarily expressed in enterocytes of the small intestine and colon [118]. As reported in Figure 3, FGF19 secretion is mainly regulated by postprandial bile acids through activation of the farnesoid X receptor (FXR). Additional regulators of FGF19 synthesis include Diet1 protein and cholesterol, and fat-soluble vitamins such as vitamins A and D [119].

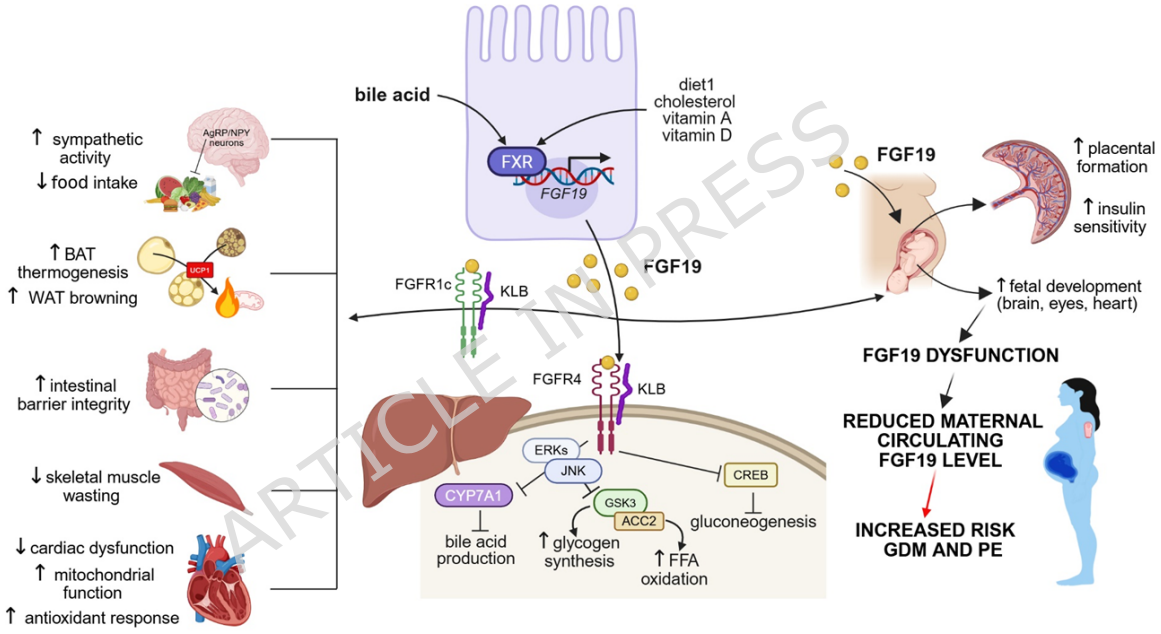

Figure 3. FGF19 as an enterokine linking bile acid signalling to systemic metabolism and GDM
FGF19 is a postprandial enterokine induced by bile acid–mediated activation of the farnesoid X receptor (FXR) in the intestine. Through interaction with FGFR4/β-klotho in the liver and FGFR1c in extrahepatic tissues, FGF19 regulates bile acid synthesis, glucose metabolism, and lipid homeostasis via ERK, JNK, and CREB signalling pathways. FGF19 also modulates energy balance, thermogenesis, and intestinal barrier integrity. In addition, emerging evidence suggests that FGF19 exerts direct cardiometabolic effects, contributing to the regulation of cardiac metabolism, mitochondrial function, and protection against stress-induced cardiac remodelling. During pregnancy, FGF19 supports placental development and insulin sensitivity, whereas reduced maternal circulating levels are associated with increased risk of GDM and PE.
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Circulating FGF19 levels typically peak 90–120 minutes after a meal, reflecting its role as a postprandial hormone acting after the early metabolic effects of insulin and glucagon [118].

FGF19 exerts its biological activity through interaction with KLB and FGF-receptors, primarily FGFR4 in hepatocytes and FGFR1c in extrahepatic tissues. FGF19 signalling mainly involves activation of MAPK, c-Jun N-terminal kinase (JNK), and cAMP response element-binding protein (CREB) signalling pathways [120].

FGF19: role in cardiometabolic health

The liver represents the principal target organ of FGF19. In hepatocytes, FGF19 downregulates cholesterol 7 alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in the classic bile acid synthesis pathway, thereby controlling bile acid production. Consistently, FGFR4-deficient mice exhibit an enlarged bile acid pool size associated with impaired JNK signalling and increased CTPA1 expression [121].

Beyond bile acid metabolism, FGF19 also influences glucose and lipid homeostasis. In experimental models, FGF19 stimulates hepatic glycogen synthesis through repression of GSK3α/β while suppressing gluconeogenesis via inhibition of the CREB. Importantly, these effects appear largely independent of insulin signalling, as AKT activation is not involved [122].

FGF19 also modulates hepatic lipid metabolism. In obese mice, FGF19 administration represses lipogenic gene expression through recruitment of DNA methyltransferases [123].

Similar to FGF21, FGF19 may also influence central appetite regulation. In obese mouse models, central administration of FGF15/19 suppresses the activity of hypothalamic agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons, thereby reducing orexigenic signalling and food intake [124]. Additional evidence suggests that stimulation of FGF15/19 expression through dietary cholesterol may also contribute to reduced food-seeking behaviour [125]. In animal models, FGF19 signalling further contributes to energy balance by enhancing sympathetic activity and promoting adipose tissue thermogenesis [126].

Experimental studies show that FGF15/19 administration increases BAT activity and induces browning of WAT [127]. Interestingly, some anti-obesity

effects of FGF19 appear to occur independently of UCP1 activation and may involve reduced intestinal lipid absorption secondary to inhibition of bile acid synthesis [128].

Recent research has also highlighted interactions between FXR/FGF19 axis and the intestinal microbiota. Activation of this pathway helps preserve intestinal barrier integrity by maintaining tight-junction integrity [129]. Conversely, reduced FXR/FGF19 signalling has been observed in individuals with prediabetes or T2D and is associated with impaired intestinal barrier function and increased inflammatory activity [130].

Beyond metabolic regulation, emerging evidence suggests that FGF19 may also influence skeletal muscle homeostasis, as reduced circulating FGF19 and Klotho proteins have been associated with sarcopenia [131, 132].

Additionally, both preclinical and clinical studies suggest that FGF15/19 exerts cardioprotective effects under conditions of metabolic stress. Experimental evidence indicates that FGF15/19 protects cardiomyocytes from hyperglycaemia-induced injury by promoting mitochondrial function and enhancing antioxidant responses [133]. In line with these findings, mice lacking FGF15 fail to develop adaptive cardiac hypertrophy in response to stress. Conversely, elevated circulating FGF19 have also been reported in patients with HF and may reflect a compensatory response associated with cardiac remodelling [134].

These data have stimulated interest in the therapeutic potential of FGF19 signalling. Engineered FGF19 analogues, such as the non-tumorigenic variant aldafermin (NGM282), have shown promising metabolic effects in clinical studies, including improvements in lipid metabolism and insulin sensitivity [135].

FGF19: pathological role in GDM

Growing evidence suggests that FGF19 contributes to placental and foetal development and that dysregulation of FGF19 signalling may occur in pregnancies complicated by metabolic disorders, such as GDM or PE [99, 136].

In experimental models of maternal obesity, overexpression or administration of FGF15/19 improves insulin sensitivity and enhances placental expression of key insulin-responsive, factors such as GLUT4 [137].

Clinical findings, however, remain less consistent. Some studies have reported lower circulating FGF19 levels in women with GDM compared with healthy pregnancies, in contrast to the increase typically observed for FGF21 [138, 139]. Nevertheless, as summarised in Table 1, not all studies have confirmed these observations.

Importantly, FGF19 also plays a role in embryonic development, contributing to the growth of organs such as the brain, eye, and heart [140-144]. In a study analysing 153 mother-infant pairs, cord plasma FGF19 levels were not significantly different between GDM and euglycaemic pregnancies. However, FGF19 levels were positively correlated with birth weight, C-peptide, and proinsulin concentrations only in female newborns, only, suggesting a potential sex-specific role of FGF19 in foetal growth regulation [145].

These findings highlight the complexity of FGF19 signalling during pregnancy and suggest that further studies are needed to clarify its potential role in GDM pathophysiology.

FGF19: response to exercise

Current evidence suggests that FGF19 is not consistently modified by aerobic exercise, whereas resistance exercise may influence its circulating levels. For example, eight weeks of moderate-intensity aerobic exercise training did not significantly alter serum FGF19 levels in women with polycystic ovarian syndrome [146], and similar results were observed in women with insulin resistance undergoing aerobic training [147]. In contrast, a randomized controlled trial reported a two-fold increase in circulating FGF19 levels three hours after resistance training in elderly men, accompanied by improvements in muscle mass and strength [148]. Conversely, other studies have observed transient reductions in FGF19 during the recovery period following exercise [149]. These heterogeneous findings suggest that FGF19 responses to

exercise may depend on multiple factors, including exercise modality, nutritional state, bile acid signalling, age, and sex.

Furthermore, it is important to note that no studies to date have specifically evaluated exercise-induced modulation of FGF19 in women with GDM, highlighting an important area for future research.

FGF19: key gaps and perspectives

Although FGF19 is increasingly recognised as an important regulator of bile acid metabolism and systemic energy homeostasis, its role in pregnancy and GDM remains only partially understood. Clinical evidence remains limited and sometimes inconsistent across studies.

Future longitudinal investigations are needed to clarify how circulating FGF19 levels fluctuate throughout pregnancy, and how these changes relate to gestational weight gain and GDM development. Given its unique role as an enterokine integrating dietary signals with systemic metabolism, FGF19 may represent an intriguing molecular link between nutrition, exercise, and metabolic adaptations during pregnancy.

FGF23: from bone hormone to GDM

Alongside liver- and intestine-derived endocrine FGFs, increasing attention is now being directed towards FGF23, a bone-derived hormone that integrates phosphate metabolism, iron homeostasis, and systemic metabolic regulation.

FGF23: cellular mechanisms of action

FGF23 is primarily synthesized by osteoblasts and osteocytes in bone in response to increased serum phosphate and 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D, also known as calcitriol), the biologically active form of vitamin D [150]. However, extra-skeletal tissues, including bone marrow stromal cells, liver, and brain, and skeletal muscle, can also produce FGF23 in response to inflammatory stimuli [151]. Moreover, experimental studies have shown that high-calorie or high-fat diets increase circulating FGF23 levels, whilst calorie restriction leads to a reduction in these levels. AMPK has been demonstrated to play a significant regulatory role in this relationship, as its activation has been shown to suppress FGF23 expression [152, 153]. In addition, insulin can

repress FGF23 expression through PI3K/Akt-mediated inhibition of the transcription factor FOXO1 [154].

In circulation, both intact FGF23 (iFGF23), the biologically active form, and C-terminal FGF23 (cFGF23), generated through cleavage by furin-like protease, can be detected. Initially, cleavage of FGF23 was considered solely a mechanism of hormonal inactivation, and cFGF23 was thought to lack biological effects [150]. However, recent evidence suggests that cFGF23 may exert biological effects, including the suppression of iron-regulating hormone hepcidin, thereby contributing to the regulation of iron homeostasis [155].

As reported in Figure 4, FGF23 mainly mediates its biological actions through interaction with α-Klotho and FGFR1. This receptor complex induces phosphorylation of fibroblast growth factor receptor substrate 2α (FRS2α), activating MAPK signalling pathway and the transcriptional activation of early growth response protein 1 (EGR1). This α-Klotho-dependent pathway is commonly referred to as canonical FGF23 signalling [156].

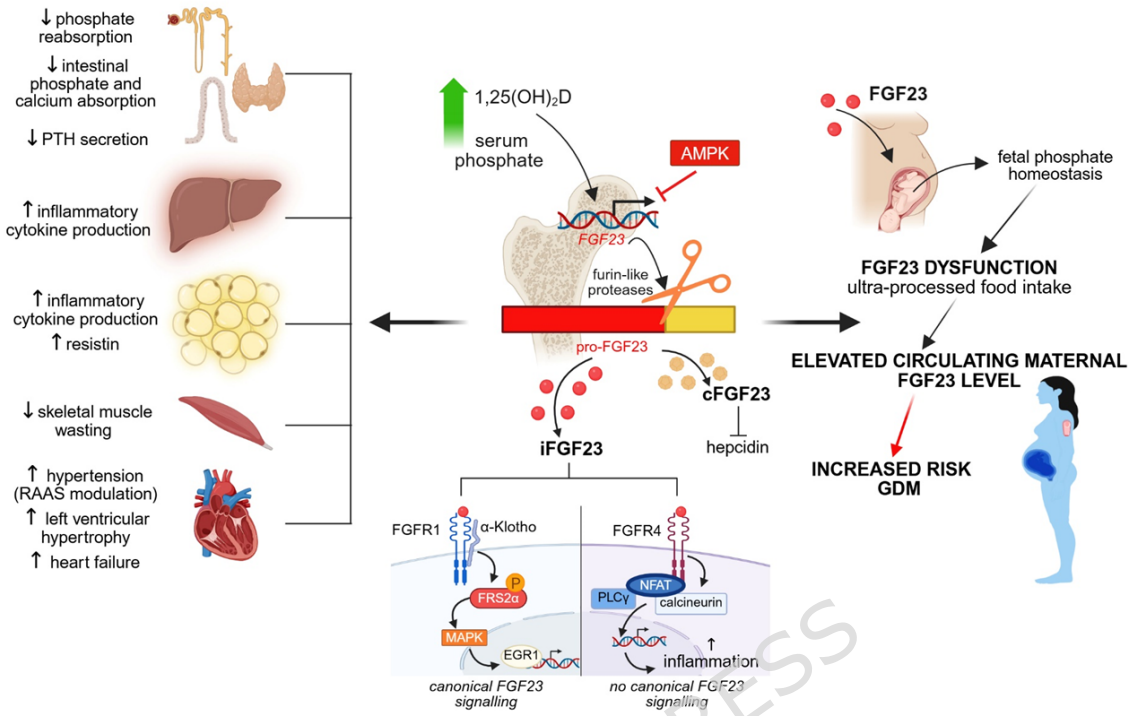

Figure 4. FGF23 signalling in mineral metabolism, inflammation, and GDM risk
FGF23 is a bone-derived hormone that regulates phosphate and vitamin D metabolism through canonical signalling via FGFR1/α-klotho and non-canonical pathways via FGFR4. Canonical signalling reduces renal phosphate reabsorption and suppresses 1,25-dihydroxyvitamin D synthesis, while non-canonical activation promotes inflammatory responses through calcineurin/NFAT signalling. Elevated FGF23 levels are associated with systemic inflammation, cardiovascular dysfunction, and metabolic disturbances. During pregnancy, increased maternal FGF23 levels, potentially influenced by dietary phosphate intake, are linked to alter foetal phosphate homeostasis and increased risk of GDM.
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In addition to its canonical endocrine actions, FGF23 can activate non-canonical signalling pathways. Experimental evidence indicates that FGF23 can bind FGFR4 independently of Klotho, triggering the calcineurin–nuclear factor of activated T cells (NFAT) and phospholipase Cγ (PLCγ) signalling cascades [157]. This pathway has been associated with inflammatory responses, as FGF23-induced activation of calcineurin signalling in hepatocytes enhances cytokine secretion [158]. Consequently, elevated FGF23 levels are frequently associated with systemic inflammatory states [159].

FGF23: role in cardiometabolic health

The primary endocrine function of FGF23 is the regulation of phosphate and calcium homeostasis. Under physiological conditions, canonical FGF23

reduces renal phosphate reabsorption and decreases circulating 1,25$(OH)_2$ D levels, thereby limiting intestinal phosphate and calcium absorption [160]. A regulatory feedback loop exists, as 1,25$(OH)_2$ also stimulates FGF23 expression [161]. In addition, FGF23 has been shown to suppress parathyroid hormone (PTH) synthesis [162].

Marked elevations in circulating FGF23 levels are hallmarks of chronic kidney disease (CKD), where impaired renal function and reduced α-Klotho expression contribute to renal FGF23 resistance and secondary alterations in mineral metabolism [164, 165].

Emerging evidence also links FGF23 to metabolic regulation and insulin resistance. FGF23 knockout mice display metabolic alterations consistent with resistance, including increased glycolysis and oxidative stress [160]. Animal models indicate that FGF23/FGFR4 signalling induces hepatic cytokine production, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), contributing to systemic inflammation [166].

Clinical evidence linking FGF23 to diabetes remains heterogeneous. Some studies report elevated circulating FGF23 levels in patients with T2D, whereas others do not observe significant differences. However, large cohort studies suggest that higher baseline FGF23 levels may independently predict the development of obesity and T2D [167]. Moreover, circulating FGF23 concentrations have been positively associated with pro-inflammatory adipokines, such as resistin, supporting the hypothesis that altered FGF23 signalling may reflect systematic inflammatory activity in metabolic diseases [168].

Preclinical studies also suggest that the pro-inflammatory actions of FGF23 may contribute to cardiovascular pathology. Upregulation of non-canonical FGF23 signalling has been associated with excessive cytokine production and activation of the FGF23/FGFR4 axis. Experimental studies indicate that cardiac tissue itself may secrete FGF23, which acts in a paracrine manner to enhance β-catenin and transforming growth factor-β (TGFβ) expression, thereby promoting myocardial fibrosis [158]. FGF23 can also activate Ca^{2+} signalling

and calcium/calmodulin-dependent protein kinase II (CaMKII) pathways, contributing to cardiac hypertrophy and electrical remodelling. Conversely, the presence of Klotho shifts FGF23 signalling toward canonical pathway, attenuating cardiac injury [169].

FGF23 also interacts with renin-angiotensin-aldosterone system (RAAS). Experimental models of CKD have demonstrated correlations between cardiac hypertrophy, myocardial FGF23 expression and RAAS-related factors [170]. Consistent with these findings, elevated circulating FGF23 levels have been associated with hypertension both in patients with CKD and in individuals without renal diseases [164].

From a translational perspective, the FGF23 pathway has already been therapeutically targeted. The monoclonal antibody, burosumab, which neutralizes circulating FGF23, is currently approved for the treatment of X-linked hypophosphatemia, highlighting the therapeutic potential of modulating FGF23 signalling [172].

FGF23: pathological role in GDM

Multiple lines of evidence highlight that circulating FGF23 levels increase during pregnancy and may be associated with gestational metabolic complications [99, 173, 174]. In a cohort study including more than 800 pregnant women, individuals who developed GDM showed significantly higher FGF23 levels compared with healthy pregnancies, independently of age and BMI. Interestingly, cord blood FGF23 concentrations did not differ between offspring of GDM and non-GDM pregnancies [175]. Experimental models further suggest that maternal FGF23 plays an important role in maintaining foetal phosphate homeostasis. In mouse models with altered FGF23 expression, maternal FGF23 appears to counteract foetal hyperphosphatemia without directly altering foetal phosphate metabolism [176, 177].

Importantly, dietary phosphate intake may represent an additional link between FGF23 signalling and GDM risk. Diets rich in ultra-processed foods (UPFs), characterized by high phosphate content, have been associated with an increased risk of GDM [178]. In experimental models, high-phosphate diets

during pregnancy induced persistent alterations in offspring phosphate metabolism and chronically elevated FGF23 and PTH levels, potentially increasing long-term cardiometabolic risk [179].

Given its pleiotropic biological actions, maintaining balanced FGF23 signalling appears essential for both maternal and foetal health.

FGF23: response to exercise

A substantial body of evidence suggests that FGF23 may also act as an exercise-responsive hormone. In the context of physiological conditions, exercise can modulate FGF23 expression and contribute to improving mitochondrial function and to reducing oxidative stress [180].

Recent studies have indicated that fluctuations in serum phosphate, induced by exercise, may contribute to the dynamic regulation of FGF23. In murine models, transient increases in circulating phosphate following exercise has been demonstrated to be associated with muscle metabolite L-β-aminoisobutyric acid (L-BAIBA), circulating FGF23 levels, and urinary phosphate excretion. These findings suggest the existence of an L-BAIBA/FGF23 axis that may be involved in cardiovascular protection against phosphate dysregulation [181].

In patients diagnosed with CDK, exercise interventions can improve bone metabolism, and partially restore the FGF23/Klotho axis, reducing circulating FGF23 levels whilst increasing Klotho expression [182]. For instance, a six-month programme of dynamic resistance training in haemodialysis patients improved bone mineral density whilst concomitantly reducing circulating FGF23 and PTH levels [183].

Lifestyle interventions combining diet and exercise have also been associated with reduced FGF23 levels in children and adolescents with overweight or obesity [184]. Furthermore, elevated FGF23 concentrations have been associated with exercise intolerance and reduced $VO2_{max}$ in patients affected by CDK or by HFpEF [184, 185].

Meta-analyses further suggest that endurance and aerobic training may help to restore the balance of FGF23/Klotho [186].

Nevertheless, the impact of exercise on FGF23 remains heterogeneous across studies, likely reflecting differences in exercise modality, metabolic status, and underlying disease. It is important to note that no studies have directly investigated the relationship between FGF23 signalling, GDM and exercise, representing a critical gap in current knowledge.

FGF23: key gaps and perspectives

Given the central importance of phosphate balance, iron metabolism, and bone-derived endocrine signals during the third trimester, the role of FGF23 in pregnancy and gestational diabetes remains only partially understood, available studies remain limited and heterogeneous.

Moreover, although emerging data suggest that exercise may influence the FGF23–Klotho axis, no studies to date have directly examined the relationship between FGF23, physical activity, and GDM. Addressing this gap could help clarify whether bone-derived endocrine signals contribute to the metabolic benefits of exercise during pregnancy.

s-Klotho at the crossroads: from FGF19s cofactor to exerkine in GDM

Beyond its well-established role as a co-factor for FGF19s, α-Klotho has emerged as an independent circulating factor involved in aging, cardiometabolic regulation, and exercise adaptation. Increasing attention has therefore focused on soluble Klotho (s-Klotho), which may exert pleiotropic protective effects across multiple metabolic tissues.

s-Klotho: cellular mechanisms of action

The α-Klotho protein exists in two different isoforms: a single-pass membrane protein and a soluble circulating form, s-Klotho, generated by cleavage of the extracellular domain of the membrane-bound protein. α-Klotho was originally discovered in klotho-mutant mice, which exhibit premature aging and multiple age-related diseases, leading to its recognition as an anti-aging factor [187]. At the molecular level, s-Klotho exerts protective actions against oxidative stress, inflammation, and fibrosis [188]. One of the best-characterized mechanisms involves the inhibition of TGF-ß signalling, a pathway implicated in fibrotic processes and in cellular senescence. Mechanistically, Klotho binds

to the type II TGF-ß receptor, suppressing downstream SMAD and MAPK signalling [188-190].

S-Klotho: role in cardiometabolic health

Experimental studies have shown that the overexpression of α-Klotho extends lifespan and reduces oxidative stress and inflammation in mice. In humans, circulating s-Klotho levels have been associated with favourable cardiometabolic profiles. For example, Amaro-Gahete FJ et al. observed in sedentary middle-aged adults a positive association between lean mass index and s-Klotho levels, together with an inverse relationship with cardiometabolic risk score [191].

At the cellular level, s-Klotho also exerts cardioprotective effects. In cardiomyocytes exposed to high glucose and in murine models of diabetic cardiomyopathy, Klotho suppressed NF-kB-mediated inflammatory signalling and enhanced antioxidant machinery through activation of Nrf2 [192, 193]. Moreover, by attenuating insulin/insulin-like growth factor-1 (IGF1) receptor, s-Klotho promotes FOXO nuclear activation and the expression of detoxifying enzymes [194].

s-Klotho: pathological role in GDM

Emerging evidence suggests that s-Klotho may also play a role in pregnancy-related metabolic disturbances. Reduced placental Klotho expression has been reported in women with T2D and was correlated with impaired mitochondrial homeostasis and increased oxidative stress. In trophoblast cells exposed to hyperglycaemic conditions, overexpression of α-Klotho restored mitochondrial function and reduced oxidative stress damage [195]. Similarly, studies in PE models have shown that Klotho-mediated activation of the Nrf2 pathway mitigates hypoxia-induced oxidative damage and cellular senescence in trophoblasts [196]. Collectively, these findings suggest that alterations in Klotho signalling may contribute to pregnancy complications characterized by oxidative stress processes also relevant.

s-Klotho: response to exercise

Exercise has consistently been shown to increase circulating s-Klotho levels [197]. A systematic review by Corrêa HL et al. concluded that exercise training significantly increases s-Klotho, supporting its emerging classification as a potential exerkine [198]. Experimental and clinical studies further support this association. Lifelong exercise in rodents reduced aging-related oxidative stress by modulating Klotho and synergistically triggering Nrf2 pathways [199], while FIT-AGEING study demonstrated that 12 weeks of exercise training increased s-Klotho levels in sedentary middle-aged adults, in parallel with improvements in body composition [200]. Higher s-Klotho levels have also been associated with improved autonomic balance, reflected by enhanced vagal activity and reduced sympathetic tone [201]. Interestingly, Neto IVS et al. investigated the intergenerational effects of paternal resistance training in Wistar rats. They observed that offspring of rats fed a high-fat diet exhibited skeletal muscle telomere shortening and altered oxidative status, which were partially mitigated by paternal exercise. Mechanistically, α-Klotho and Keap1, a key negative regulator of Nrf2, were identified as mediators of these exercise-induced adaptations [202]. To date, however, no comparable studies have been performed in female models, representing an important knowledge gap, particularly in the context of GDM.

s-Klotho: key gaps and perspectives

Overall, evidence supports a protective role of Klotho in cardiometabolic regulation and exercise adaptation, but its role in GDM remains largely unexplored. Most studies derive from non-pregnant or male models, leaving key gaps in maternal and intergenerational contexts. Future studies should determine whether Klotho acts as both a biomarker and a mediator, linking exercise to metabolic health during pregnancy.

Adipsin beyond immunity: an emerging cardio-metabolic modulator of GDM

Adipsin, also known as Complement factor D (CFD), is a serine protease essential for the activation of the alternative complement system pathway. Through the generation of complement factor-3 fragment a (C3a), the adipsin-

C3a axis contributes to communication between adipose tissue and metabolic organs, particularly pancreatic islets [203].

Adipsin: cellular mechanisms of action

Adipsin, predominantly secreted by mature adipocytes, is a key enzymatic component of the alternative complement pathway. At the cellular level, adipsin cleaves complement factor B in the presence of C3b, leading to the formation of C3 convertase and the subsequent generation of the bioactive fragments C33a and C3b (Figure 5).

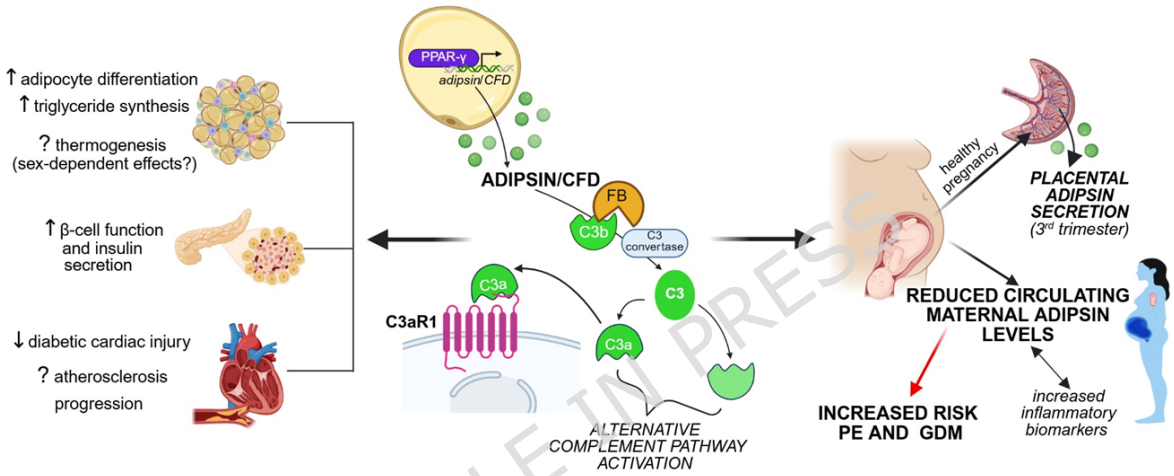

Figure 5. Adipsin (CFD) and complement-mediated metabolic regulation in GDM
Adipsin (complement factor D) is an adipokine that activates the alternative complement pathway, leading to the generation of C3a and subsequent signalling through C3aR1. This pathway links adipose tissue to pancreatic β-cell function, enhancing insulin secretion and contributing to metabolic homeostasis. Adipsin also regulates adipocyte differentiation and energy metabolism, with potential cardioprotective effects. During pregnancy, placental adipsin contributes to maternal circulating levels, whereas reduced adipsin concentrations are associated with increased inflammatory markers and higher risk of GDM and PE.
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Beyond its classical immunological function, the interaction of adipsin-derived C3a with its receptor C3aR1 has emerged as an important signalling pathway linking adipose tissue to systemic metabolic homeostasis [204, 205].

Adipsin: role in cardiometabolic health

Growing evidence indicates that adipsin plays a relevant role in pancreatic β-cell function. Several studies, including loss-of-function animal models, have shown that adipsin promotes secretion and contributes to preservation of β-cells mass and function [206]. In line with these findings, Gómez-Banoy N et

al. reported that adipsin overexpression significantly attenuates pancreatic islet atrophy in a mouse model of T2D with β-cell failure [207].

Beyond its effects on pancreatic function, recent evidence indicates that the adipsin/C3a/C3aR1 axis also contributes to the regulation of adipose tissue metabolism. Adipsin promotes adipocyte differentiation and lipid accumulation, at least in part through inhibition of Wnt/β-catenin signalling. Ma L et al. revealed that adipsin/C3a/C3aR1 axis regulates adaptive thermogenesis in a sex-dependent manner. Specifically, female adipocyte-specific C3aR1-knockout mice displayed impaired brown adipose tissue thermogenesis and cold intolerance, likely reflecting lower expression of adipsin and C3aR1 in adipose depots [208].

Human studies investigating the metabolic role of adipsin have yielded heterogeneous results. Circulating adipsin levels are frequently elevated in individuals with obesity and positively correlate with BMI and with leptin levels, suggesting that increased adipsin expression may represent a compensatory response to metabolic stress [209, 210]. According to this hypothesis, in early stages of T2D, high circulating levels of adipsin may contribute to glucose and lipid homeostasis, whereas disease progression and β-cell failure are associated with declining adipsin levels [205, 211].

However, not all studies confirm a consistent association between adipsin levels and glucose intolerance, suggesting that cohort heterogeneity, small sample size, differences in disease stage, and pharmacological treatments may contribute to these discrepancies.

Also, evidence from animal models remains controversial regarding the role of adipsin in atherosclerosis. In *ApoE*$^{-/-}$ mice fed a high-cholesterol diet, adipsin appears to inhibit atherosclerotic plaque formation, whereas in *Ldlr*$^{-/-}$ mice fed a diet-induced obesity regimen, adipsin deficiency does not significantly influence atherosclerosis progression [212, 213].

By contrast, consistent evidence supports a cardioprotective role of adipsin in the context of metabolic stress, as adipsin overexpression partially alleviates diabetes-associated coronary microvascular damage [214-216].

Adipsin: pathological role in GDM

Emerging data suggest that adipsin may also be involved in GDM. Circulating adipsin levels fluctuate during pregnancy, typically increasing from early to late gestation [217-219]. Placental macrophages (Hofbauer cells) are able to secrete adipsin, highlighting a potential contribution of placental cells to maternal circulating levels. In a cross-sectional study, McElwain CJ et al. observed that pregnancies complicated by obesity and GDM are characterized by elevated placental adipsin secretion [217].

Prospective data further support a link between adipsin levels and GDM risk. In a cohort of 1660 pregnant women, Cai M et al. measured circulating adipsin levels at 12 weeks of gestation and reported significantly lower levels in women who later developed GDM compared with controls [218]. However, other population-based studies have reported the opposite trend, with higher adipsin concentrations in women with GDM during late pregnancy [219]. These conflicting findings may reflect differences in gestational timing, adiposity, and inflammatory status.

Notably, several studies have proposed adipsin as a potential biomarker for PE, further supporting its role in pregnancy complications [220].

Adipsin: response to exercise

A growing body of evidence shows that exercise may influence adipsin secretion. In diet-induced obese male mice, exercise training counteracts the increase in adipsin expression induced by diet [221]. Similarly, 12 weeks of treadmill exercise improves insulin sensitivity and modulates the bone marrow microenvironment, partly through mechanosensitive pathways associated with the reduced adipsin expression [222].

Human studies also support exercise-related modulation of adipsin. Long-term physical activity has been associated with changes in circulating adipsin concentrations [223], and the combination of resistance training with alternate-day calorie restriction reduced both body weight and adipsin in individuals with obesity [224].

Adipsin: key gaps and perspectives

Despite growing evidence supporting a role for adipsin in metabolic regulation, several aspects of its biology remain incompletely understood. In particular, its role in pregnancy and gestational diabetes requires further investigation.

Future studies should clarify how adipsin signalling interacts with visceral adipose tissue expansion, placental production, and systemic inflammation across different stages of pregnancy. In addition, the temporal dynamics of circulating adipsin levels and their relationship with β-cell function and insulin resistance in GDM remain to be fully elucidated.

Moreover, although emerging evidence suggests that exercise may modulate adipsin signalling, the mechanisms underlying this interaction and its relevance in pregnancy are still poorly defined. Understanding whether adipsin represents not only a biomarker but also a mediator linking adipose tissue, complement activation, and metabolic adaptation may provide new insights into cardiometabolic risk in GDM.

Limitations and future perspectives

The concept of exerkines, has emerged as a framework to explain how exercise exerts systemic metabolic and cardiovascular effects through endocrine signalling pathways. Emerging evidence suggests that several exerkines may contribute to the pathophysiology of (GDM) and are represent promising targets for future investigation.

While specific limitations for individual exerkines have been discussed in the previous sections, several common challenges emerge across the field.

Current knowledge of the exerkine network in GDM remains fragmentary and limited by important methodological constraints. Experimental studies specifically addressing exercise-induced modulation of exerkines in GDM models remain scarce, with most available data being derived from murine models of obesity or T2D. Although these models have limited translational relevance, they provide fundamental insights into maternal and offspring molecular adaptations to exercise and their potential long-term cardiometabolic implications. For instance, studies by Sun C et al. [105], Shan M et al. [116], and Neto IVS et al. [202] suggest that exercise-induced

modulation of specific exerkines may exert lasting effects on offspring metabolic health.

Clinical evidence remains similarly limited. Studies investigating circulating exerkines during pregnancy are generally restricted to specific time points, most often at GDM diagnosis or at delivery, and are usually confined to basal conditions, without direct evaluation of structured exercise interventions. Expanding this evidence base is therefore essential not only to clarify the molecular mechanisms underlying GDM but also to explore whether exerkine profiles may contribute to more personalised exercise-based strategies.

Another limitation concerns the narrow scope of current analyses, as most studies investigate only a limited subset of exerkines. Advances in high-throughput omics technologies may enable a more comprehensive characterisation of the exerkines network, and support the integration of artificial intelligence–based approaches for improved maternal and offspring cardiometabolic risk stratification.

The interaction between exercise and nutrition in shaping exerkine responses also represents an underexplored yet highly relevant area of research. Several exerkines are influenced not only by physical activity but also by dietary factors. Members of FGF19s subfamily provide an illustrative example, as their expressions are regulated by diet, including bile acids or phosphate intake, and, are also involved in central appetite regulation. In this context, emerging pharmacological strategies targeting endocrine FGFs, including FGF21 and FGF19 analogues or mimetics, may offer additional opportunities that should be investigated.

Importantly, alterations in several of these exerkines have also been associated with an increased risk of PE, suggesting the existence of shared pathophysiological mechanisms across pregnancy-related cardiometabolic complications. A deeper understanding of these common pathways may help to identify integrated biomarkers and therapeutic targets relevant to both GDM and PE.

Finally, future research should aim to clarify the mechanistic role of these molecules in the pathophysiology of GDM and their contribution to intergenerational cardiometabolic risk. Emerging evidence also indicates that several exerkines are detectable in human milk across different stages of lactation, from colostrum to mature milk, suggesting that their biological relevance may extend beyond pregnancy and highlighting lactation as an additional window of metabolic and cardiovascular programming deserving further investigation [225]. In this context, exercise may represent a biological modulator of endocrine pathways capable of influencing maternal and offspring cardiometabolic trajectories.

Conclusions

In conclusion, emerging exerkines, including chemerin, adipsin, and members of the FGF19 family, may represent components of a complex endocrine network linking exercise, metabolism, and cardiometabolic health in GDM. However, the current body of evidence in pregnancy remains limited and heterogeneous, and the mechanistic role of these molecules is not yet fully defined.

Notwithstanding the aforementioned limitations, this field represents a promising and as yet underexplored area in maternal–foetal medicine. Advancements in omics technologies have the potential to facilitate a more comprehensive characterisation of the exerkine network. In this context, exercise, which is frequently underutilised in clinical practice, has the capacity to act not only as a behavioural intervention but also as a biological modulator of endocrine pathways, with potential implications for cardiometabolic prevention in both mothers and offspring.

List of Abbreviations

1,25(OH)$_2$ D : 1,25-dihydroxyvitamin D

ATF4: activating transcription factor 4

AgRP: agouti-related peptide

AMPK: AMP-activated protein kinase

Nrf2: anti-oxidative response promoting nuclear

BAT: brown adipose tissue

NFAT: calcineurin–nuclear factor of activated T cells

CaMKII: calcium/calmodulin-dependent protein kinase II

ChREBP: carbohydrate response element-binding protein

CVD: cardiovascular diseases

CCRL2: CC motif chemokine receptor-like 2

CMKLR1: chemerin-like receptor 1

CYP7A1: cholesterol 7 alpha-hydroxylase

CKD: chronic kidney disease

JNK: c-Jun N-terminal kinase

KLB: cofactor β-klotho

CFD: complement factor D

C3: complement factor-3

CREB: cAMP response element-binding protein

DCM: diabetic cardiomyopathy

DNMT3A: DNA methyltransferase 3A

EGR1: early growth response protein 1

ERK: extracellular signal-regulated kinase

FXR: farnesoid X receptor

FGFR4: FGF Receptor 4

FGF19s: FGF19 family

FRS2α: fibroblast growth factor receptor substrate 2α

FFA: free fatty acids

GPR1: G protein-coupled receptor 1

GDM: Gestational diabetes mellitus

GLP-1: Glucagon-like peptide-1

HF: heart failure

HFpEF: heart failure with preserved ejection fraction

HIIT: high intensity interval training

IL-6: interleukin-6

LVH: left ventricular hypertrophy

L-BAIBA: L-β-aminoisobutyric acid

MASH: metabolic dysfunction-associated steatohepatitis

MAPK: mitogen-activated protein kinase

MICT: moderate-intensity continuous training

NPY: neuropeptide Y

NF-κB: nuclear factor-κB

PTH parathyroid hormone

PGC-1α peroxisome proliferator-activated receptor gamma coactivator 1- α

PPARγ peroxisome proliferator-activated receptor γ

PPARα peroxisome proliferator-activated receptor-α

PLCγ phospholipase Cγ

PE preeclampsia

RAAS renin-angiotensin-aldosterone system

SIRT1 sirtuin 1

SHP Small Heterodimer Partner

TGFβ transforming growth factor-β

FGFRs transmembrane tyrosine kinase FGF receptors

T2D type II diabetes

UCP1 uncoupling protein 1

VTA ventral tegmental area

VMH ventromedial hypothalamus

WAT white adipose tissue

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

P.S. and A.M.: conceptualization, bibliographic research, review and editing.

P.S.: original draft preparation and writing.

A.S., F.A., E.C., and L.L.: Discussion, review and editing.

All authors approved the current version of the manuscript.

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Table 1. Human studies investigating circulating exerkines in gestational diabetes mellitus (GDM) versus normal glucose tolerance (NGT)

This table summarizes human studies in which at least one of the selected molecules (chemerin, FGF19s family, and adipsin) was measured in women with GDM compared with women with normal glucose tolerance (NGT). As of early March 2026, a total of 102 studies were identified in the literature. Studies were included following qualitative selection criteria, excluding those with major methodological limitations or potential sources of bias, and retaining only those reporting at least the timing of biomarker assessment during pregnancy or the peripartum period. Although several findings have been supported by subsequent meta-analyses, the available evidence remains highly heterogeneous. In particular, substantial variability is observed in sample size across groups, as well as in the timing of measurement and study design. These limitations highlight the need for future well-standardized studies with harmonized protocols to improve comparability and strengthen conclusions in this field.

Year of Publication	DOI	Sample Size (GDM/NTG)	Study Period	Chemerin Comparison GDM vs NTG
2025	10.1016/j.cyto.2025.157057	38/122	First-trimester analysis	No difference
2023	10.3390/ijms25010175	84/90	At the time of diagnosis	↑
2021	10.1016/j.gene.2021.145888	303/221	At the time of diagnosis	↑
2021	10.1016/j.tjog.2021.05.019	22/29	At the time of diagnosis	No difference
2021	10.1155/2021/5547228	153/84	At the time of diagnosis	↑
2021	10.1155/2021/553380	53/43	During second trimester	↓
2021	10.1017/S2040174421000118	33/33	At the time of diagnosis	↑
2021	10.3803/EnM.2020.831	22/20	At the time of diagnosis	No difference
2021	10.1371/journal.pone.0242423	50/100	During first trimester	↑
2020	10.1136/bmjdrc-2020-001333	214/107	During early and mid-pregnancy	↑
2020	10.1016/j.cyto.2020.155088	74/74	At the time of diagnosis	No difference
2019	10.1002/dmrr.3114	48/225	At the time of diagnosis	No difference
2017	10.1080/01443615.2017.1385596	46/43	At the time of diagnosis	↑
2018	10.1016/j.peptides.2018.01.005	15/23	At the time of the Cesarean section	↑
2017	10.1016/j.metabol.2017.08.003	52/73	At the time of diagnosis	No difference
2017	10.12659/msm.903565	140/140	At the time of diagnosis	↑
2017	10.1080/09513590.2017.1320382	19/20	During first trimester	↑

2017	10.1080/14767058.2016.1199671	208/300	During first trimester	↑
2014	10.1016/j.ando.2014.10.001	48/42	At the time of diagnosis	↑
2014	10.1111/dme.12436	9/68	During third trimester	↓
2012	10.3109/14767058.2012.686540	69/62	At the time of the Cesarean section	No difference
Year of Publication	**DOI**	**Sample Size (GDM/NTG)**	**Study Period**	**FGF21 Comparison GDM vs NTG**
2023	10.1155/2023/4024877	74/32	At the time of diagnosis	↑
2023	10.1002/dmrr.3717	332/664	During first trimester	↑
2022	10.1111/jdi.13889	62/58	At the time of diagnosis	↑
2021	10.3389/fendo.2021.630287	133/133	Early second trimester	↑
2019	10.1016/j.bbrc.2019.03.034	29/33	During third trimester	↑
2018	10.33549/physiolres.934017	12/12	At the time of diagnosis	no difference
2015	10.1007/s00592-014-0705-9	79/78	During third trimester	↑
2014	10.1007/s12020-014-0309-8	51/50	At the 28th week	↑
2013	10.1371/journal.pone.0081190	30/60	At the time of diagnosis	↑
2013	10.1371/journal.pone.0065254	12/12	At the time of diagnosis	↑
Year of Publication	**DOI**	**Sample Size (GDM/NTG)**	**Study Period**	**FGF23/Adipsin Comparison GDM vs NTG**
2023	10.1002/dmrr.3704	64/762	At the time of diagnosis	cFGF23↑
2018	10.20945/2359-3997000000070	54/33	At the time of diagnosis	FGF23↑

2017	10.1590/2359-3997000000287	46/36	At the time of diagnosis	FGF23↑
2025	10.1186/s12933-025-02744-2	178/1465	At the time of diagnosis	Adipsin↑
2024	10.1210/clinem/dgad699	26/30	At the time of diagnosis	Adipsin↑
2023	10.1016/j.gene.2023.14722	200/200	At the time of diagnosis	Adipsin no difference

Legends of Figures

Figure 1. Chemerin signalling in cardiometabolic regulation and GDM
Chemerin is an adipose tissue–derived signalling molecule that primarily acts through CMKLR1 (ChemR23), with additional binding to GPR1 and CCRL2, activating downstream MAPK, PI3K/AKT, and NF-κB pathways. These signalling cascades underlie its effects on adipocyte differentiation, insulin sensitivity, lipid metabolism, and vascular function. In addition, emerging evidence indicates that chemerin contributes to the regulation of energy balance and food intake. During pregnancy, placental-derived chemerin supports vascular remodelling, whereas dysregulated signalling and elevated circulating levels are associated with adverse outcomes, including GDM and PE.
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Figure 2. FGF21 as a stress-responsive exerkine in metabolic adaptation and GDM
FGF21 is a liver-derived endocrine factor induced by nutritional stress (e.g. fasting, ketogenic diet, and macronutrient imbalance) through transcriptional regulators including PPARα, ATF4, and ChREBP. Acting via the FGFR1c/β-klotho complex, FGF21 activates downstream pathways, including AMPK signalling, promoting fatty acid oxidation, thermogenesis, insulin sensitivity, and antioxidant responses. Notably, FGF21 stimulates adiponectin secretion from adipose tissue, which acts as a key downstream mediator amplifying its systemic metabolic effects. During pregnancy, FGF21 contributes to adaptive metabolic responses, while elevated circulating levels, particularly in early gestation, are associated with increased risk of GDM and PE.
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Figure 3. FGF19 as an enterokine linking bile acid signalling to systemic metabolism and GDM
FGF19 is a postprandial enterokine induced by bile acid–mediated activation of the farnesoid X receptor (FXR) in the intestine. Through interaction with FGFR4/β-klotho in the liver and FGFR1c in extrahepatic tissues, FGF19

regulates bile acid synthesis, glucose metabolism, and lipid homeostasis via ERK, JNK, and CREB signalling pathways. FGF19 also modulates energy balance, thermogenesis, and intestinal barrier integrity. In addition, emerging evidence suggests that FGF19 exerts direct cardiometabolic effects, contributing to the regulation of cardiac metabolism, mitochondrial function, and protection against stress-induced cardiac remodelling. During pregnancy, FGF19 supports placental development and insulin sensitivity, whereas reduced maternal circulating levels are associated with increased risk of GDM and PE.

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Figure 4. FGF23 signalling in mineral metabolism, inflammation, and GDM risk

FGF23 is a bone-derived hormone that regulates phosphate and vitamin D metabolism through canonical signalling via FGFR1/α-klotho and non-canonical pathways via FGFR4. Canonical signalling reduces renal phosphate reabsorption and suppresses 1,25-dihydroxyvitamin D synthesis, while non-canonical activation promotes inflammatory responses through calcineurin/NFAT signalling. Elevated FGF23 levels are associated with systemic inflammation, cardiovascular dysfunction, and metabolic disturbances. During pregnancy, increased maternal FGF23 levels, potentially influenced by dietary phosphate intake, are linked to alter foetal phosphate homeostasis and increased risk of GDM.

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Figure 5. Adipsin (CFD) and complement-mediated metabolic regulation in GDM

Adipsin (complement factor D) is an adipokine that activates the alternative complement pathway, leading to the generation of C3a and subsequent signalling through C3aR1. This pathway links adipose tissue to pancreatic β-cell function, enhancing insulin secretion and contributing to metabolic homeostasis. Adipsin also regulates adipocyte differentiation and energy metabolism, with potential cardioprotective effects. During pregnancy, placental adipsin contributes to maternal circulating levels, whereas reduced adipsin concentrations are associated with increased inflammatory markers and higher risk of GDM and PE.

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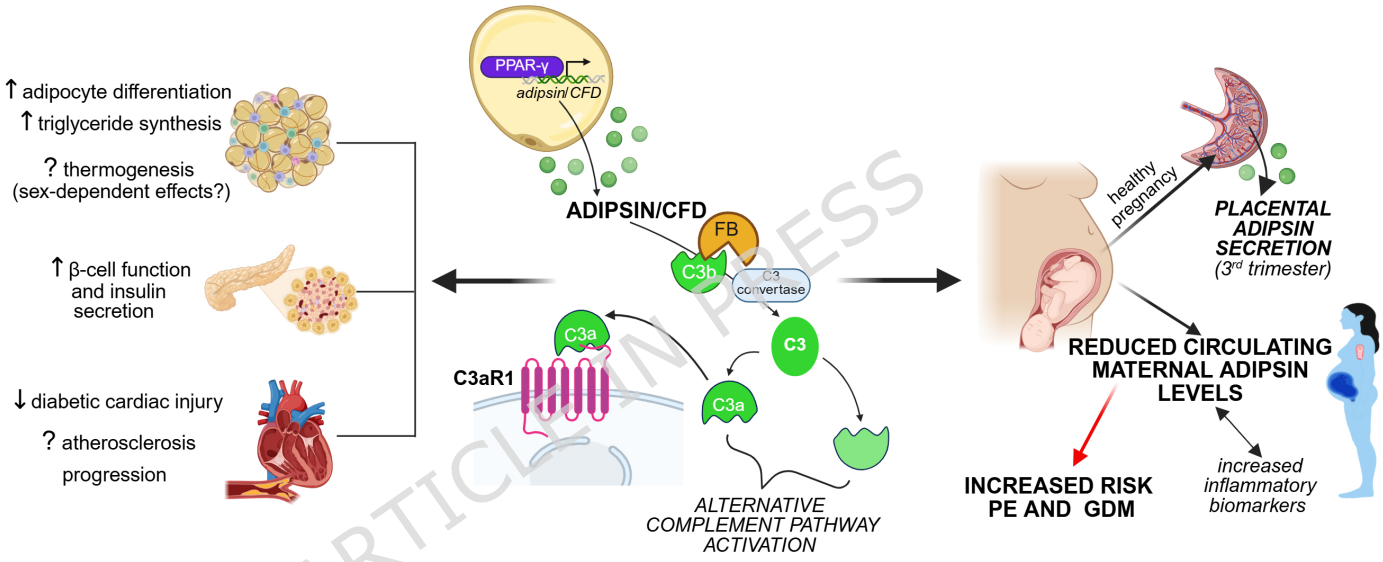
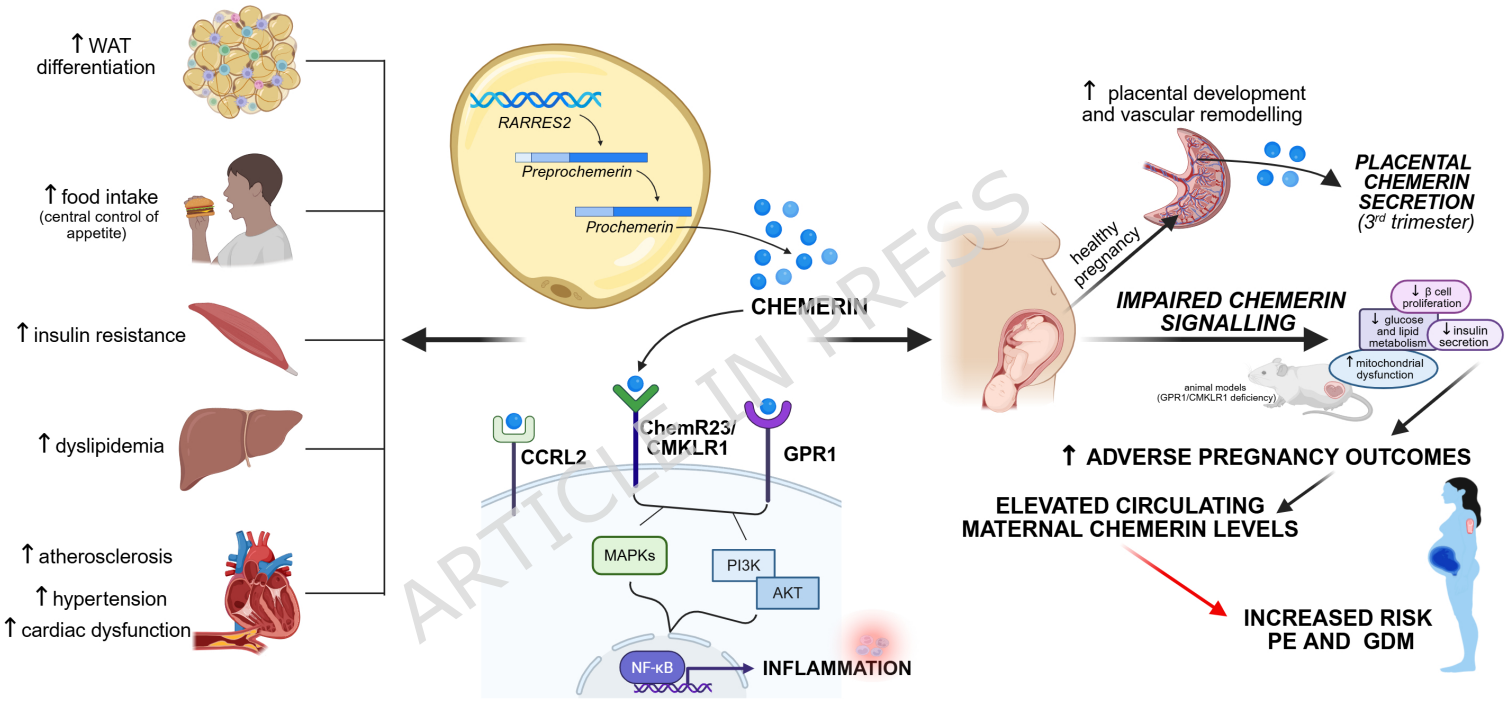
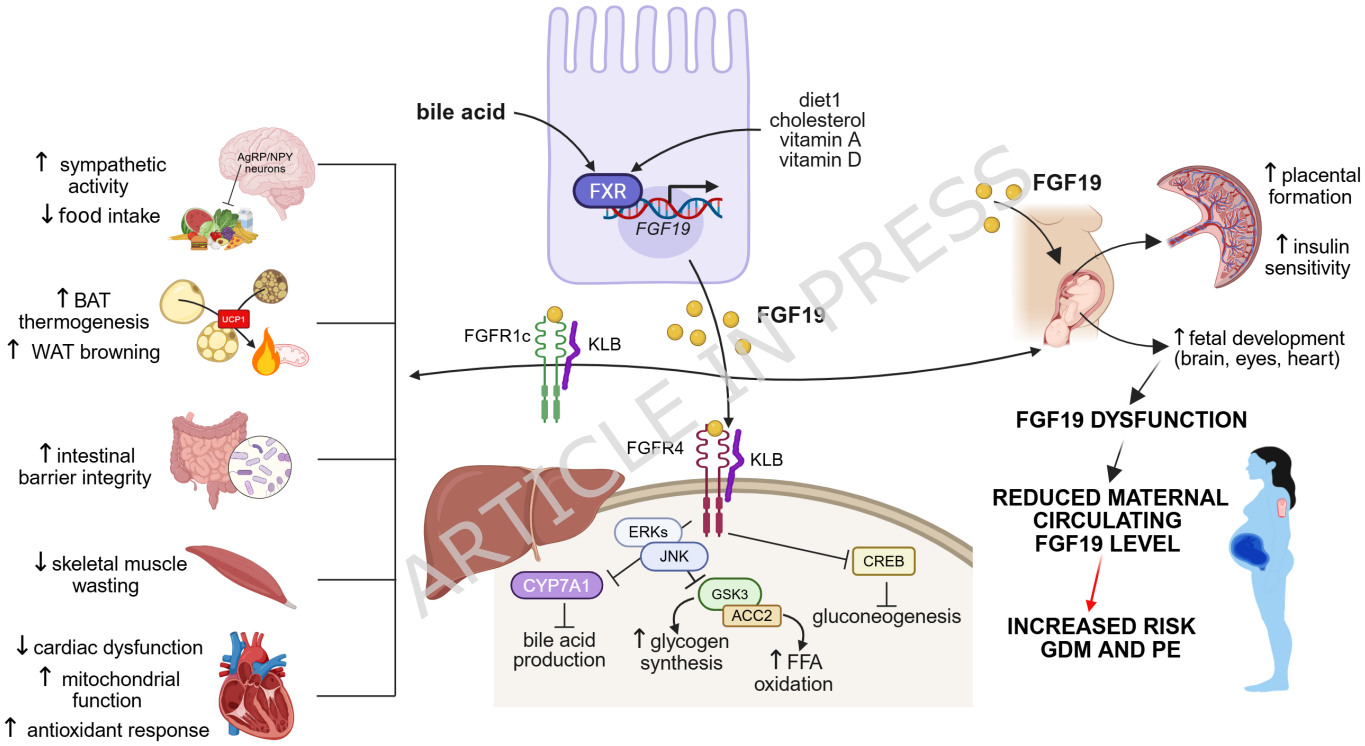
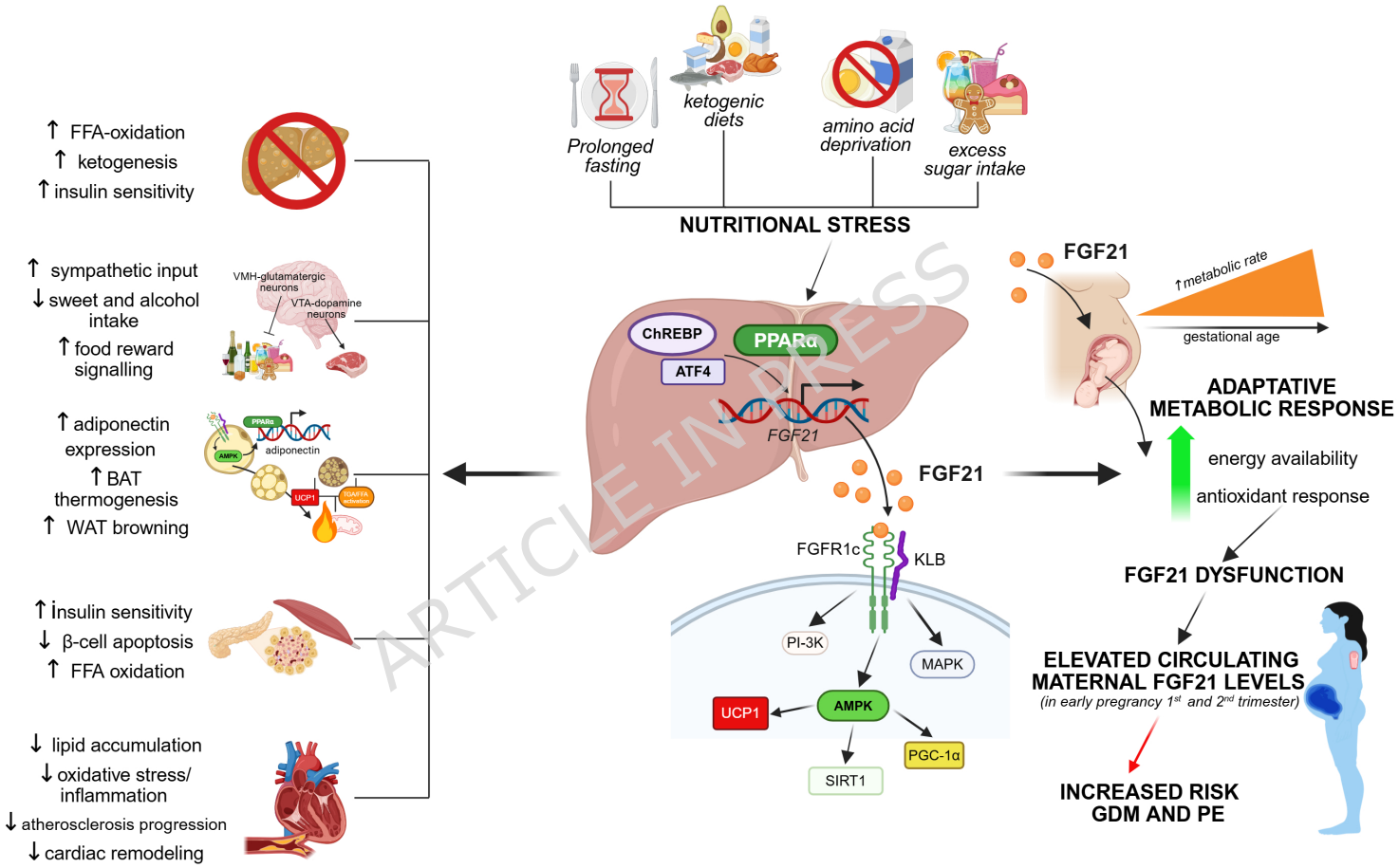
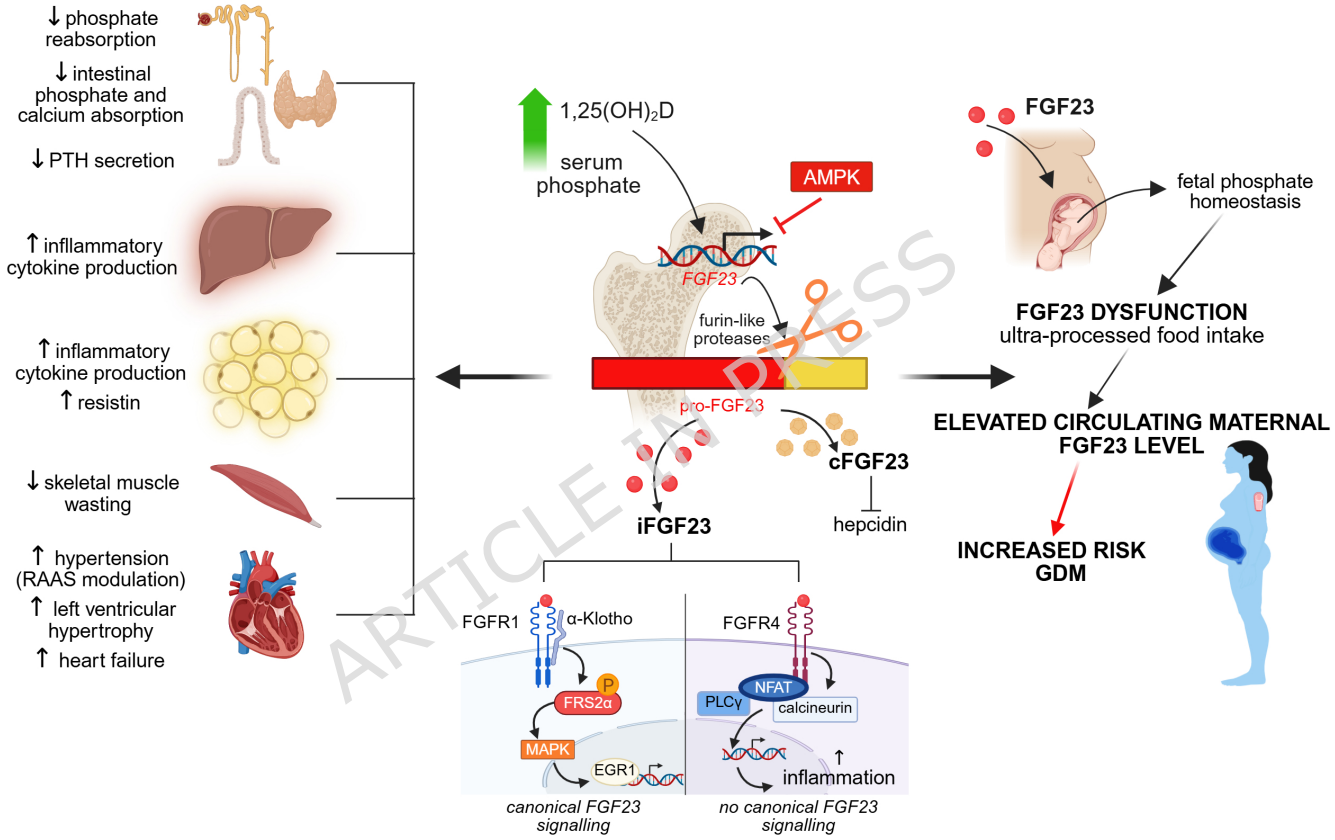


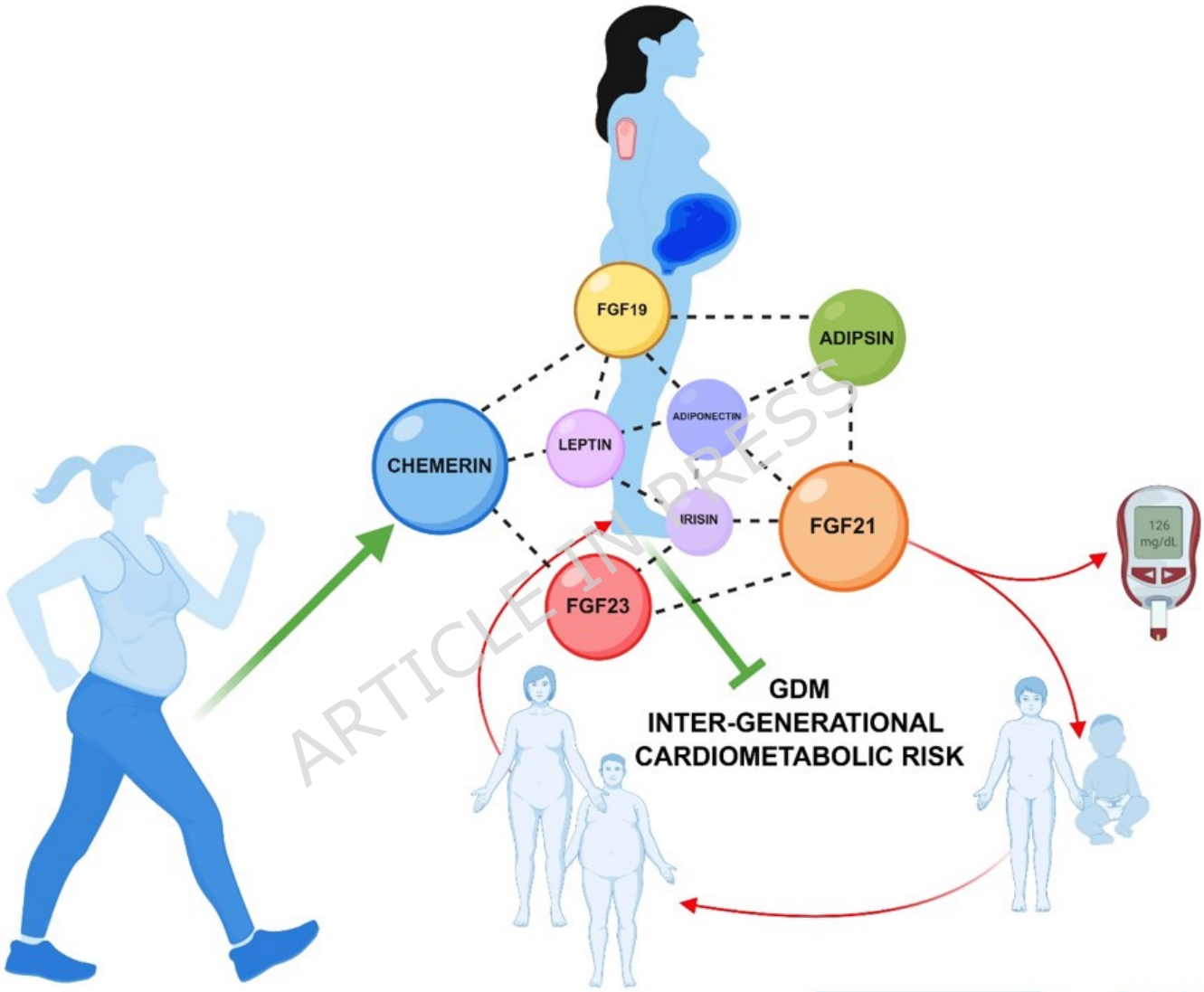








Mapping the exerkines network as a promising tool to address inter-generational cardiometabolic risk in GDM: a narrative review



14% GDM global prevalence

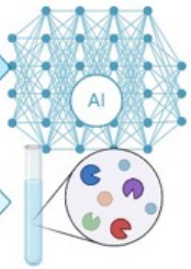
↑ T2D and CVD for mother and offsprings

Exercise is a GDM therapy

Mapping EXERKINES NETWORK

↑ GDM MANAGMENT

↑ T2D-CVD STRATIFICATION RISK



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Gestational Diabetes as an inter-generational cardiometabolic risk factor: spotlight on emerging exerkines

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Table 1. Human studies investigating circulating exerkines in gestational diabetes mellitus (GDM) versus normal glucose tolerance (NGT)

This table summarizes human studies in which at least one of the selected molecules (chemerin, FGF19s family, and adipsin) was measured in women with GDM compared with women with normal glucose tolerance (NGT). As of early March 2026, a total of 102 studies were identified in the literature. Studies were included following qualitative selection criteria, excluding those with major methodological limitations or potential sources of bias, and retaining only those reporting at least the timing of biomarker assessment during pregnancy or the peripartum period. Although several findings have been supported by subsequent meta-analyses, the available evidence remains highly heterogeneous. In particular, substantial variability is observed in sample size across groups, as well as in the timing of measurement and study design. These limitations highlight the need for future well-standardized studies with harmonized protocols to improve comparability and strengthen conclusions in this field.

Year of Publication	DOI	Sample Size (GDM/NTG)	Study Period	Chemerin Comparison GDM vs NTG
2025	10.1016/j.cyto.2025.157057	38/122	First-trimester analysis	No difference
2023	10.3390/ijms25010175	84/90	At the time of diagnosis	↑
2021	10.1016/j.gene.2021.145888	303/221	At the time of diagnosis	↑
2021	10.1016/j.tjog.2021.05.019	22/29	At the time of diagnosis	No difference
2021	10.1155/2021/5547228	153/84	At the time of diagnosis	↑
2021	10.1155/2021/553380	53/43	During second trimester	↓
2021	10.1017/S2040174421000118	33/33	At the time of diagnosis	↑
2021	10.3803/EnM.2020.831	22/20	At the time of diagnosis	No difference

2021	10.1371/journal.pone.0242423	50/100	During first trimester	↑
2020	10.1136/bmjdrc-2020-001333	214/107	During early and mid-pregnancy	↑
2020	10.1016/j.cyto.2020.155088	74/74	At the time of diagnosis	No difference
2019	10.1002/dmrr.3114	48/225	At the time of diagnosis	No difference
2017	10.1080/01443615.2017.1385596	46/43	At the time of diagnosis	↑
2018	10.1016/j.peptides.2018.01.005	15/23	At the time of the Cesarean section	↑
2017	10.1016/j.metabol.2017.08.003	52/73	At the time of diagnosis	No difference
2017	10.12659/msm.903565	140/140	At the time of diagnosis	↑
2017	10.1080/09513590.2017.1320382	19/20	During first trimester	↑
2017	10.1080/14767058.2016.1199671	208/300	During first trimester	↑
2014	10.1016/j.ando.2014.10.001	48/42	At the time of diagnosis	↑
2014	10.1111/dme.12436	9/68	During third trimester	↓
2012	10.3109/14767058.2012.686540	69/62	At the time of the Cesarean section	No difference
Year of Publication	**DOI**	**Sample Size (GDM/NTG)**	**Study Period**	**FGF21 Comparison GDM vs NTG**
2023	10.1155/2023/4024877	74/32	At the time of diagnosis	↑
2023	10.1002/dmrr.3717	332/664	During first trimester	↑
2022	10.1111/jdi.13889	62/58	At the time of diagnosis	↑
2021	10.3389/fendo.2021.630287	133/133	Early second trimester	↑

2019	10.1016/j.bbrc.2019.03.034	29/33	During third trimester	↑
2018	10.33549/physiolres.934017	12/12	At the time of diagnosis	no difference
2015	10.1007/s00592-014-0705-9	79/78	During third trimester	↑
2014	10.1007/s12020-014-0309-8	51/50	At the 28th week	↑
2013	10.1371/journal.pone.0081190	30/60	At the time of diagnosis	↑
2013	10.1371/journal.pone.0065254	12/12	At the time of diagnosis	↑
Year of Publication	**DOI**	**Sample Size (GDM/NTG)**	**Study Period**	**FGF23/Adipsin Comparison GDM vs NTG**
2023	10.1002/dmrr.3704	64/762	At the time of diagnosis	cFGF23↑
2018	10.20945/2359-3997000000070	54/33	At the time of diagnosis	FGF23↑
2017	10.1590/2359-3997000000287	46/36	At the time of diagnosis	FGF23↑
2025	10.1186/s12933-025-02744-2	178/1465	At the time of diagnosis	Adipsin↑
2024	10.1210/clinem/dgad699	26/30	At the time of diagnosis	Adipsin↑
2023	10.1016/j.gene.2023.14722	200/200	At the time of diagnosis	Adipsin no difference