The Impact of Gestational Diabetes Mellitus on the Composition of Breast Milk: A Systematic Review

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Abstract. Gestational diabetes mellitus (GDM) is a pregnancy complication that affects the health of both the infant and maternal. Breast milk is the optimal food for the infant, including nutrients that support the infant's physical metabolism and biologically active components that help the infant's functional development. This article is a systematic review of published literature on the effects of GDM on the component of mother's milk. This review analyzed a total of 28 articles reporting a total of 83 breast milk constituents associated with GDM, 37 of which were biologically active. In conclusion, GDM may change human milk composition but the paucity of studies and the considerable heterogeneity of their designs and methods make it difficult to draw reliable and relevant conclusions.

Keywords: Gestational Diabetes Mellitus; Human Milk Composition; Breastfeeding; Lactation; Infant; Systematic Review.

1. Introduction

The risk of developing gestational diabetes mellitus (GDM) during pregnancy tends to increase with socio-economic development, changes in people's lifestyles and diets, increasing gestational age and number of pregnancies, as well as changes in the diagnostic criteria for GDM. Wothers with GDM and their offspring have a higher risk of suffering from metabolic diseases than the progeny of healthy mothers [1,2,3,4].Breastfeeding is considered to be an important intervention for GDM, and pregnant mothers with GDM are encouraged to complete at least three months of breastfeeding [5]. The benefits of breastmilk for infants are derived from the essential nutrients, microorganisms, and bioactive components necessary for infant growth and development, such as immunoglobulins, hormones, lactoferrin protein, active cellular components, growth factors, oligosaccharides and microRNA [6,7]. However, the composition of human milk can change based on the mother's health conditions, dietary nutritional status, metabolic abnormalities, and pathologies such as GDM [8].

Research on the mother's milk composition is still topical, but mostly in healthy populations and cross-sectional studies, with less focus on its disease state and dynamic changes. Although several results on the effect of GDM on mothers and newborns have been described, few studies have effectively described the impact of this pathological condition on the components of lactation and whether these changes pose an immediate or long-term adverse health risk to offspring [9,10]. Peila et al. reviewed the effects of diabetes on breast milk composition; moreover, they did a comprehensive review of the influence of GDM on human milk composition[11]. To provide more scientific feeding advice to mothers with GDM, the scientific community should continue to research the interactions between maternal factors, breast milk composition, and infant health.

In order to provide a more comprehensive explanation of the possible impact of GDM on neonatal development and breast milk nutrition, this review synthesises the latest research on the breastmilk ingredients among women with GDM and analyses the results with respect to seven component categories: energy, protein, lipids, carbohydrates, vitamins, minerals, and biologically active substances.

2. Method and Materials

A systematic review of the Pubmed, Web of Science, Science Direct and Scopus databases for full-text papers on human subjects published in English before 30 November 2022. We used the MeSH terms gestational diabetes mellitus, gestational, diabetes, women, female, human, milk, breast milk, colostrum, and lactation.

3. Results

3.1 Study Selection

A total of 3840 articles were identified. After excluding 461 duplicate articles, 90 full-text articles were remained. Sixty-two records were excluded for three reasons. The first is that the type of article is a review or meta-analysis, the second is that the topic of the study does not match, and the third is that the studies with unclear diabetes status and other diseases (Figure 1).

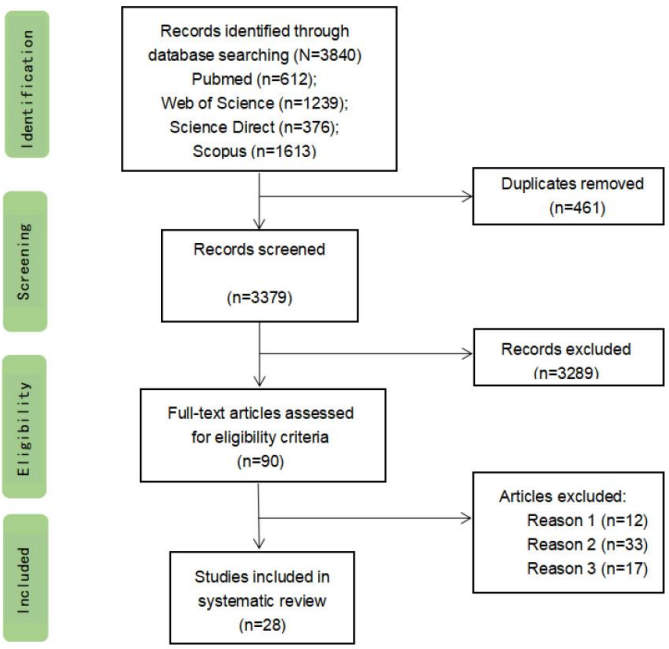


Figure 1. Flow diagram showing the different phases of the review

3.2 Information about Included Studies

The 28 articles included in this systematic evaluation were published between January 1, 2002 and December 31, 2022. Relevant information is summarised in Table 1.

Abbreviations: R, Reference; CTL, Control; GA, Gestational Age; Sample Storage- Temp, Sample Storage Temperature; Col, Colostrum; Trans, Transitional milk; Mat, Mature milk; d, day; w, week; m, month; T, Term; PT, Preterm; NE, Not Evaluated; HE, Hand Expression; PE, Pump Expression; EBP, Electric Breast Pump; HGBP, Hospital grade breast pump; MP, Manual breast pump.

Table 1. Details of the included studies.

R	Sample size(GDM:CTL)	Sample collection Timing	GA	Treat-ment	Analysis Method	Sample collection method	Sample Storage - Temp
12	20:20	Col:0-1d	T	NE	Different methods for different substances	NE	-20℃
13	12:14	Col:2d Mat:15d	T	Diet	Commercially available RIA kit	NE	-70℃
14	10:10	Col:2d	T	Diet	ELISA	NE	NE

		Mat:15d					
15	17:116	Col:1-3d	T	Diet Insulin	Gasometry apparatus	HE	NE
16	37:133	Col:7d Mat:3m	T	Diet	Radioimmunoassay and electrochemiluminescence immunoassay	HE EBP	-80°C
17	8:16	Trans:2w	T	NE	mass spectrometry and Bradford assay	HGBP	-80°C
18	20:31	Col:1d	T PT	NE	High-performance liquid chromatography	HE	-18°C
19	15:15	Col:1d Trans:7d Mat:15d	T	NE	ELISA and EIA	NE	-40°C
20	12:12	Col:1d Trans:7d Mat:20d	T	NE	ELISA and EIA	NE	-80°C
21	21:47	Col:1-4d Mat:6w	T	Diet Insulin	High-performance liquid chromatography	NE	NE
22	6:12	Col:1-3d	T	Diet Insulin	chromatography tandem mass spectrometry	HE	-80°C
23	19:47	Col:2-5d Mat:3m	T	NE	Real-time PCR	NE	-80°C
24	27:183	Col:0-5d Trans:6-14d Mat:>14d	PT	Diet	Human milk analyzer(HMA, MIRIS, Uppsala, Sweden)	EBP	0-4°C
25	29:34	Col:1-5d	T	NE	Gas chromatographic	HE MBP	-70°C
26	12:21	Col:1-2d Mat:30d	NE	NE	ELISA	HE	-80°C
27	48:48	Col:3d Mat:42,90d	T	NE	ELISA	EBP	-80°C
28	33:33	Col:1-3d Mat:42d	NE	NE	ELISA	MBP	-80°C
29	31:31	Col:3d Trans:7d Mat:14d	T	Diet Medic-ations	MIRIS milk analyzer	HE	-20°C
30	13:22	Col:1d,>2d	T	Insulin	ELISA	PE	-35°C
31	90:94	Col:1-3d Trans:7-10d Mat:4w	T	NE	Gas chromatography-mass spectrometry (GC-MS)	PE	-80°C
32	26:27	Col:1-5d Trans:7-10d Mat:15-17d	T	Diet	ELISA	NE	-80°C
33	44:460	Mat:2.6±0.4m	T PT	NE	ELISA	HE	NE
34	36:155	Col:5±2d Trans:10±2d Mat:4±0.5m	PT	NE	ELISA	HGBP	-80°C
35	50:50	Col:1-3d Trans:10d Mat:42d	T	NE	Liquid chromatography tandem mass spectrometry	PE	-80°C
36	45:45	Col:1-5d	T	NE	Liquid Chromatography TandemMass Spectrometry	HE	-80°C
37	15:24	Mat:10-12w	T	NE	Gas chromatography	HGBP	-80°C
38	35:154	Mat:1m±5d; 3m±10d	T	NE	ELISA	HGBP	-80°C
39	14:11	Col:1-2d	T	NE	Luminex	HE	-80°C

3.3 Collection of Breast Milk Samples

There are three stages of lactation: colostrum, transitional milk, and mature milk. Colostrum is produced from delivery to 5 days postpartum. Transitional milk is produced from 6 to 15 days postpartum, while mature milk is produced from 15 days postpartum to weaning [40,41]. Colostrum has been studied most frequently, with 23 published studies [12,13, 14,15,16, 18,19, 20,21, 22,23, 24, 25, 27,28,29,30,31,32,34,35, 36,39]. In contrast, the transitional milk stage has been the least studied, with only nine published studies [17,19,20,24,29,31,32,34,35]. The timing of mature milk collection varied widely, with researchers performing breast milk collection from postnatal day 14 [29] through the fourth month [34].

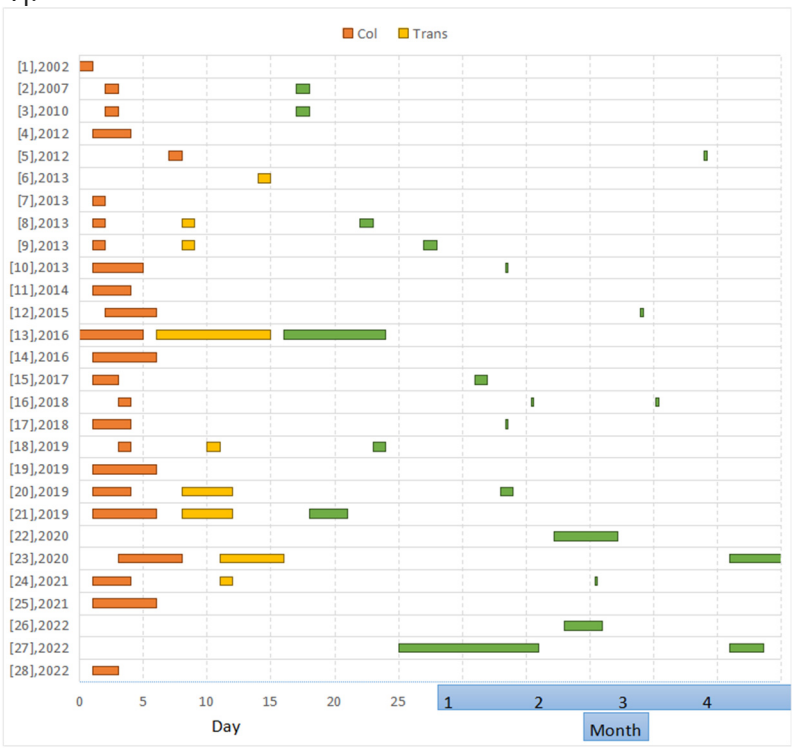


Figure 2. The times and types of human milk sample collection.

3.4 The Effect of Gestational Diabetes Mellitus on the Composition of Human Milk

Twenty-eight studies demonstrating the results of the effect of GDM on the components of human milk in table 2. This subsection has divided into eight parts to analysis: energy, protein, lipids, carbohydrates, vitamins, minerals, biologically active substances, and the metabolome.

Table 2. The relationship between GDM and human milk components

Breast milk composition		R	Reference
Energy		↑ N ↓	Col/Trans/Mat:[24] Col/Trans:[29] Mat:[29]
Protein	Total protein content	N ↓	Col:[12,24,29]; Trans/Mat:[29] Trans:[17]; Trans/Mat:[24]
Protein types	Apolipoprotein, Prostasin, Ig heavy chain V−II region ARH-77	↑	Col:[22]
	Alpha-2-HS-Glycoprotein,Apolipoprotein A1,Apolipoprotein E, 14−3−3 Protein zeta/Delta, Protein disulfide-isomerase, Protein DJ-1, Protein FAM3B	↓	Col:[22]

	Total FAA		N	Col/Mat:[21]
	Amino Acid	N-methyl-D-aspartic acid, L-serine acid, D-glutamic acid	↓	Mat:[35]
	Total lipids contetnt		N ↓	Col/Trans:[24,29] ; Mat:[24] Col:[12] ; Mat:[29]
	Triglycerides		N	Col:[12]
	Cholesterols		N	Col:[12]
	Fatty acid	Total MUFA	N	Mat:[37]
		Linoleic Acid(C18:2)	↑	Mat:[37]
		lauric Acid (C12:0)	↓	Mat:[37]
		Eicosatrienoic Acid	↑	Col:[25]; Mat:[35]
		γ-linolenic Acid, Arachidonic, Docosatetraenoic Acid	↑	Col:[25]
		LysoPC (22:6)	↑	Mat:[35]
		LysoPC (18:2)	↑ ↓	Mat:[35] Trans:[35]
Carbohydrates	Total Carbohydrate		N	Col/Trans/Mat:[24]
	Lactose		N ↓	Col/Trans/Mat:[29] Col:[12]
	HMOs		N	Trans:[17]
	Monosaccharides	Glucose	N ↓	Col:[12] Mat:[38]
		Iditol, Galactitol, Sorbitol	↓	Mat:[35]
Vitamin	α-Tocopherol		N	Col:[18]
	Riboflavin		↑	Trans/Mat:[35]
	Pantothenic acid		↑	Trans/Mat:[35]
	Pyridoxal		↑	Trans/Mat:[35]
		4-pyridoxic	↑	Col/Trans/Mat:[35]
Mineral	Potassium, Phosphorus, Calcium		N	Col:[12]
	Sodium		↑	Col:[12,15]

Biological active substance	hormones	Insulin	↑ N ↓	Col/Mat:[27] Col/Mat:[16,26] Mat:[38]
		Insulin-like Growth Factor-1	N	Col/Trans/Mat:[34] ;Mat:[33]
		Ghrelin	N ↓	Mat:[13,14] Col:[13,14]; Col/Mat:[27]
		Adiponectin	N ↓	Col/Mat:[16,26] ,Mat:[33,38] Col/Mat:[27], Col/Trans/Mat:[34]
		Leptin	N	Col/Mat:[26,27],Mat:[33,38],Col/Trans/Mat:[34];
		Irisin	N ↓	Mat:[19]; Col/Mat:[28] ,Col/Trans:[19]
		Apelins-12/36, Nesfatin-1	N ↓	Mat:[14] Col:[14]
		adropin	N ↓	Trans/Mat:[19] Col:[19]
		Copeptin	N ↑	Trans/Mat:[19] Col:[19]
		Preptin	N ↑	Trans/Mat:[20] Col:[20]
		Salusin-α	N ↓	Trans/Mat:[20] Col:[20]
		Salusin-β	N ↓	Mat:[20] Col/Trans:[20]

	Pro-hepcidin, hepcidin-25	N ↑	Mat:[20] Col/Trans:[20]
	SREBP1-c	N	Col:[28]
	Chemerin, Dermicin	↑	Col/Trans/Mat:[32]
Cytokines and Growth factors	IL-10, IFN-g, IL-15	↑	Col:[39]
	IL-6	N ↑	Mat:[38] Col:[39]
	IL-4	N	Col:[39]
	IL-1ra	↓	Col:[39]
	VEF, FGF-basic, PDGF, G-CSF	N	Col:[39]
	GM-CSF	↓	Col:[39]
Bioactive Proteins	sIgA	N ↓	Col:[12] Trans:[17]
	sialic acid N-glycans	↓	Trans:[17]
	Lactoferrin	↑	Trans:[17]
	lactoferrin total N-glycans	↑	Trans:[17]
	NGAL	N	Col:[30]
	NGAL/MMP-9	↑	Col:[30]
	C-reactive protein	↑	Mat:[38]
Micro RNA		N	Col/Mat:[23]

Abbreviations: FAA, free amino acids; N, no difference; ↓, lower; ↑, higher.

3.4.1 Energy

The two analyses from Dritsakou et al. and Shapira et al. reported different results regarding energy at three stages of lactation. Dritsakou et al. found that GDM would elevate energy values at each stage. . However, another study indicated that GDM only affected mature milk, decreasing its energy content, while colostrum and transitional milk were not affected [29].

3.4.2 Protein

In total, eight studies explored the possible effects of GDM on total protein content, protein categories, amino acids, and free amino acids in mother's milk. Four studies investigated total protein in milk. Three articles on colostrum all indicated that no statistical differences were found between the the two groups [12,24,29]. Shapira et al. found that GDM also did not affect transitional or mature milk [29]. In contrast, Dritsakou et al. found that GDM reduced the total protein content in both stage [24]. Meanwhile, this finding was supported by a study on transitional milk only [17].

The other four studies used proteomics techniques or metabolomics for detection. Two of these articles explored the types of proteins in colostrum. Of the 601 proteins identified by Grapov et al., 260 were subjected to further analysis. Ultimately, 27 proteins were identified as the most predictive of GDM, and concentrations of and 10 of these proteins were determined to be significantly different between the two groups after correction for multiple testing.Three of these proteins had elevated levels due to this pathological condition and seven had reduced concentrations [22]. In another study, a total of 1295 proteins were detected, 192 of which showed significantly different concentrations in the the two groups. These 192 proteins were associated with carbohydrate, pro-inflammatory, and lipid metabolism [36]. In addition, using the same technique, Klein et al. found that the the concentration of free amino acids in colostrum and mature milk was not affected by GDM [21]. Finally, Wu et al. showed that GDM reduced the levels of three non-essential amino acids in mature milk,N-methyl-D-aspartic acid, L-serine, and D-glutamic acid respectively [32]. It is noteworthy that four studies included experimental groups that experienced dietary or pharmacological treatment during pregnancy [21,22,24,29].

3.4.3 Fat

A total of six studies investigated the total lipid content, triglycerides, cholesterol, and fatty acids(FA) in human milk in the GDM and control groups. Three studies explored total lipid content, and two of these examined all three stages of lactation. Neither of the two studies found any statistical differences in colostrum or transitional milk in two goups[24,29]. Nevertheless, they found conflicting results in mature milk, with Dritsakou et al. showing no significant difference and Shapira et al. concluding that GDM reduces the total lipid content. Moreover, Kaushik et al. analysed only colostrum and found that the GDM group had lower total lipid concentrations than the control group [12]. Also their results showed that GDM did not affect triglyceride and cholesterol levels in colostrum of GDM patients.

The other three studies explored the fatty acid content in breast milk. Sarkadi et al. analysed only mature milk and found higher levels of linoleic acid (C18:2) and lower levels of lauric acid (C12:0) in the milk in the GDM group, whereas total MUFA did not appear to be affected by this pathological condition [37]. Chertok et al. examined colostrum only and found that GDM increased the levels of γ-linolenic acid, arachidonic acid, docosatetraenoic acid, and eicosatrienoic acid in breast milk [25]. Similarly, Wu et al. found elevated levels of eicosatrienoic acid in mature milk from mothers with GDM [35]. They also found higher concentrations of LysoPC(22:6) and LysoPC(18:2) in mature milk from mothers with GDM than from the control group and lower levels of LysoPC(18:2) in the transitional.

3.4.4 Carbohydrates

Six articles explored the concentration of total carbohydrate content, lactose, human milk oligosaccharides (HMO) and monosaccharides in the human milk.One study examined the total saccharides level of mother's milk, finding no significant difference at any stage of breastfeeding. For the analysis of lactose in breast milk, Kaushik et al. found that GDM reduced lactose concentrations in colostrum [12], while Shapira et al. indicated no statistical difference was found throughout compared with the control group[29]. Moreover, there was no difference between the two groups for the level of HMO in the transition milk[17]. Otherwise, three studies examined monosaccharides in breast milk. Two studies examined glucose, with Choi et al.found that GDM reduced glucose concentrations in colostrum [38], while Kaushik et al. stated that GDM did not affect glucose in mature milk [12]. Additionally, using metabolomics techniques, Wu et al. found that GDM reduced the concentrations of iditol, galactitol, and sorbitol in breast milk [35].

3.4.5 Vitamins

Only two studies have examined vitamins in breast milk. Resende et al. examined alpha-tocopherol levels in colostrum and found no significant statistical between GDM and health groups [18]. Wu et al. investigated B vitamins and found higher concentrations of pantothenic acid, riboflavin, and pyridoxal in the transitional and mature milk of women with GDM than in the health group. Moreover, they found that 4-pyridoxic, a metabolite of pyridoxal, was the only substance that was higher in the GDM group in all three stages [35].

3.4.6 Minerals

Two studies have analysed the macronutrients in mother's milk. Kaushik et al. found that GDM did not affect potassium, phosphorus and calcium concentrations in colostrum, but did increase sodium levels [12]. Galipeau et al. supports the results regarding sodium[15].

3.4.7 Biologically Active Substances

A total of 17 studies have examined the association of GDM with Biological active substance in breast milk. Due to the wide range of biological components, for convenience of understanding we have classified its into four types according to the function: hormones, cytokines and growth factors, bioactive protein and micro RNA.

3.4.7.1 Hormones

A total of 12 studies explored the relationship between GDM and metabolic hormone concentrations in breast milk, including insulin, insulin-like growth factor-1 (IGF-1), ghrelin, adiponectin, leptin, irisin, apelins-12/36, nesfatin-1, adropin, copeptin, salusin-α, salusin-β pro-hepcidin, hepcidin-25, SREBP1-c, chemerin, and dermicin. Four studies tested insulin concentrations in breast milk, with inconsistent results. Of the three studies that examined colostrum and mature milk, one indicated that GDM increased insulin concentrations [27] and the other two suggested no effect [16,26]. In contrast, Choi et al. suggested that it would decrease concentrations in mature milk [38].In addition, two studies have examined IGF-1 levels in breast milk and both indicated that GDM had no effect on it[33,34]. Three studies tested ghrelin concentrations in the milk. Two studies indicated that GDM reduced ghrelin values in colostrum, but had no effect on mature stage [13,14]. However, Yu et al. showed that GDM reduced ghrelin concentrations in both colostrum and mature milk[27].

Six studies reported adiponectin concentrations in breast milk, all using ELISA assays except for Ley et al. [16]. Two studies found that GDM reduced the level of lipocalin in human milk [27,34]. Notably, one study subject gave birth prematurely [34] and the other was treated with diet or insulin during pregnancy [27]. Interestingly, Galante et al. found that mothers with GDM whose offspring were male had the lowest concentrations of lipocalin in breast milk of all groups, and this result was independent of daughter born to women with GDM and those born to control subjects [33]. However, after correcting for the duration of exclusive breastfeeding, the gender difference became non-significant ($p = 0.05$). Infant gender may influence the alteration of lipocalin in breast milk by GDM, but further studies are needed to determine this.

Five studies explored leptin concentrations in breast milk and none found any significant differences in the two group [26,27,33,34,38]. Two studies analysed the tevel of irisin in human milk. Aydin et al.de stated that GDM reduced irisin levels in the first two lactation stages but did not affect the last stage [19]. They also found that irisin concentrations increased in all three stages. This result is partially contradicted by the findings of Chertok et al. This study, which considered maternal BMI, indicated that GDM reduced its contents in colostrum and mature milk [25].

Five articles reported for the first time several hormones associated with GDM. One study found that GDM reduced the level of apelins-12, apelins- 36, and nesfatin-1 in colostrum, but no influence on mature stage [14]. In addition, Aydin et al. indicated that GDM does not alter the concentration of adropin, Copeptin in either transitional or mature milk. However, in colostrum, Aydin et al. found that GDM decreased the level of adropin but increased the level of copeptin [19]. Furthermore, the same group of researchers found in another study that GDM decreased salusin-α and salusin-β concentrations, while increasing preptin, pro-hepcidin, and hepcidin-25 values in early lactation, but there was no change in late lactation [20]. In addition, Fatima et al. examined SREBP1-c concentrations in colostrum and found no differences between GDM and control groups [28]. Finally, Ustebay et al. analysed chemerin and dermicin and found that its concentrations were higher in the breast milk of patients with GDM than in the health women [32].

3.4.7.2 Cytokines and Growth Factors

Two studies have explored the relationship between GDM with Cytokines and Growth factors. De Sena Avellar et al. used Luminex analysis on colostrum and showed that GDM did not affect VEF, FGF-basic, PDGF , G-CSF and IL-4 values but decreased IL-1ra and GM-CSF levels.They also found increased concentrations of IL-6, IL-10, IL-15 and IFN-g in the colostrum in GDM group [39]. In addition, they found higher levels of most cytokines and chemokines, such as pro-inflammatory and anti-inflammatory factors, in the first stage of GDM group than in control group. Choi et al. also examined IL-6 in breast milk and found no association between IL-6 in mature milk and GDM status after adjusting for demographics, maternal factors, and diet [38]. This outcome may be related to the lower receptor concentration of IL-6 in the third stage compared to colostrum the poorer affinity of the receptor [42,43].

3.4.7.3 Bioactive Proteins

Four studies reported seven bioactive proteins in breast milk. Smilowitz et al. tested transition milk and indicated that GDM decreased the concentration of sIgA and sialic acid N-glycans as well as increased the concentration of Lactoferrin and lactoferrin total N-glycans [17]. In addition, one study indicated that GDM had no effect on the concentration of sIgA in colostrum [12].Moreover, Metallinou et al. found that GDM did not modify NGAL levels in colostrum, but increased NGAL/MMP-9 values [30]. The last study investigated C-reactive protein (CRP) and showed increased concentrations in the GDM group during the mature milk stage [38]. However, this study lacked postnatal glucose data to evaluate the association of postnatal glucose intolerance with CRP concentrations in breast milk.

3.4.7.4 MicroRNA

To date, one research has examined Micro RNA and the results indicate that GDM has no impact on colostrum and mature milk [23].

3.4.8 Metabolome

Two studies used metabolomic assays for the three stages of lactation in the GDM and control groups, with consistent gestational cycles, collecting and storing of samples. Wen et al. identified 187 metabolites, with 58 metabolites significantly different within the GDM group, and 28 metabolites between the two groups [23].

Wu et al. identified 620 metabolites and classified them into nine patterns of variation for further analysis [35]. Ultimately, 38 compounds were found to exhibit significant differences in pattern shifts between the two groups. Furthermore, they found that GDM had a stronger influence on the metabolome of mature milk than on the metabolome of colostrum or transition milk. However, this study did not take into account the association between clinical parameters of the infant and maternal serum and breast milk metabolites.

4. Discussion

The main finding is that GDM can influence breast milk components. This review provides a comprehensive overview of the different components of human milk in association with GDM in 28 articles. Relatively few researches have examined the effects of GDM on energy and macro-nutrients in breast milk; however, the existing data suggest that GDM may change the energy, total protein content, and total lipid content, as well as the level of lactose and glucose in mother's milk. However, GDM does not appear to affect the total saccharides in milk. Only four studies have reported very limited data on 2 vitamins and 4 minerals. Evidence suggests that B vitamins and sodium by GDM. In contrast, 17 studies have detected a total of 37 bioactive substances in the milk of women with GDM; however, the impact of GDM on its is inconclusive. In studies with a small number of participants and follow-ups within one month of delivery, the differences associated with GDM were mainly detected in early breast milk. Overall, the pathological condition of GDM may affect both the nutrients and non-nutrients in mother's milk.

Because of the mostly exploratory approach of the included studies, the small amount of experimental data, and differences in study design and methodology, this review cannot draw definitive conclusions about the affects of GDM on the component of human milk. The studies considered in this review also had several limitations. First, most of the studies had small sample sizes, while studies with larger sample sizes had greater differences in sample size between groups.Small and unequal sample sizes reduced the statistical power of the analyses, making it difficult to detect significant differences between GDM and control groups. Second, the target population is poorly represented in these studies. The components of milk is constantly changing and is affected by numerous variables; however, few studies have considered geographical and dietary differences, or the influence of maternal health status, genetics, age, dietary nutritional status, stage of lactation, or environmental factors on breast milk. All of these factors may interact with GDM in

undetermined ways, thus obscuring the relationship between GDM and breast milk composition. Third, the heterogeneity in study designs, timing and method of sample collection, and definition and analysis of different lactation stages complicated our interpretation of the study results. Furthermore, few studies collected or considered sufficient ancillary information on variables. Finally, although infant exposure to GDM in womb may increase their future risk of metabolic diseases, most studies do not collect the volume of mother's milk ingested by infants. Therefore, it is not possible to accurately assess the health effects of maternal GDM on breastfeeding infants when few if any influencing factors are considered.

This retrospective study is the most recent comprehensive review of the impact of GDM on human milk composition. In 2019, Peila et al. conducted a review of the effects of diabetes mellitus on breast milk composition during pregnancy [11]. Our review incorporates the most recent findings on the topic, in particular including the addition of data on biologically active substances. They summarised 39 substances regarding GDM, while this review reported 80 items. In contrast to reviews that focused on only one type of substance in breast milk, such as that by Suwaydi et al. who examined the effects of GDM on hormones [19]; however, this review evaluated the association between GDM and breast milk from a multidimensional perspective. Moreover, this review considered variations in study design and methodology, which are important factors that have been largely overlooked in previous reviews, such as the method and timing of sample collection, sample storage environment, and comparison table of sample collection times.

In light of the current state of research, we recommend that additional studies be conducted in several areas to promote the health of mothers with GDM and their infant. First, although some studies have expanded the variety of milk components examined and have broadened the geographic and demographic scope of their studies to more accurately represent the population of mothers and infants with GDM, the difficulty of randomly sampling this population has resulted in a lack of globally representative data on the effects of GDM on the mother's milk. Multi-country collaborations should be encouraged to develop such studies, which should also examine the dynamic effects of GDM on variations in milk ingredients throughout the different stages of lactation and the health effects on the offspring.

Second, because genetic, dietary, and environmental factors maycombine with this pathological condition to influence the altered components of mothers' milk, future study designs should take such a comprehensive, holistic approach, researchers to improve the accuracy. Third, with the advancement of experimental techniques, "novel" components of breast milk are being identified. The functions of both novel and known components of GDM breast milk should be explored from multiple perspectives, including in vitro and animal experiments, as well as epidemiological and clinical studies.Finally, at the implementation stage, a collaborative platform for breast milk research and the construction of a breast milk data warehouse could hasten the achievement of research goals. However, a prerequisite to integrating different studies is the standardisation of research methods, diagnostic criteria for GDM, definitions of lactation stages, and analytical techniques.

5. Conclusion

There are limited available literature on related topics and these provide preliminary evidence that GDM affects breast milk composition; however, it is difficult to quantify this impact or the impact of these effects on the immediate and long-term health of the infant. Future research on the impacts of GDM on human milk and the influence of those impacts on mother and infant well-being should incorporate a more comprehensive approach, a standardised experimental design, and larger sample sizes to ensure high-quality results, with the ultimate target of achieving optimal nutritional status and health status for maternal and offspring.

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