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Colostrum and mature breast milk analysis of serum irisin and sterol regulatory element-binding proteins-1c in gestational diabetes mellitus

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Colostrum and mature breast milk analysis of serum irisin and sterol regulatory element-binding proteins-1c in gestational diabetes mellitus

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ABSTRACT

Background: We aimed to evaluate irisin and SREBP-1c levels in serum, colostrum and mature breast milk in women with and without gestational diabetes (GDM); and to relate them with maternal glucose, lipid profile and weight status of babies.

Methods: GDM positive women ($n = 33$) and normal glucose tolerant women (NGT) ($n = 33$) were recruited. Maternal blood samples were collected at 28th week of gestation and later at 6-week post-partum while breast milk samples of the lactating mothers were collected within 72 hours of birth (colostrum) and at 6 weeks post-partum (mature milk). Irisin and SREBP-1c levels were analyzed by commercially available ELISA kits for all maternal samples.

Results: Lower levels of irisin were seen in serum, colostrum and mature breast milk of GDM females ($p < .01$). SREBP-1c profile showed a similar trend of low serum levels in GDM, however, they were undetectable in colostrum and mature breast milk. Weak to moderate correlations of serum irisin with BMI ($r = 0.439$; $p < .001$), GTT 0 hours ($r = 0.403$; $p = .01$), HbA1c ($r = -0.312$; $p = .011$), Fasting blood glucose ($r = 0.992$; $p = .008$), and baby weight at birth ($r = 0.486$; $p < .001$). Colostrum and mature breast milk irisin showed positive associations with baby weight at 6 weeks ($r = 0.325$; $p = .017$; $r = 0.296$; $p = .022$, respectively). Serum SREBP-1c at 6 weeks correlated with ~~the baby weight ($r = 0.255$; $p = .039$),~~ random blood glucose ($r = 0.318$; $p = .009$), and HbA1c ($r = -0.292$; $p = .011$). All correlations were lost once we adjusted for maternal BMI.

Conclusions: Low irisin and SREBP1-c levels may favor development of GDM in pregnant subjects. Further, low mature breast milk levels may act as a continued stressor from fetal to infant life as long as breast-feeding is continued. Further studies are required to identify the mechanistic relationship between these biomarkers and GDM.

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Mature breast milk; cytokine; obesity; gestational diabetes; irisin; SREBP

Introduction

Gestational diabetes mellitus (GDM) is a growing pandemic in the world. At least 17.8% of women are being affected by this condition worldwide [1]. GDM is often accounted for by increased levels of maternal hormones during pregnancy ensuring adequate energy supply to the fetus like estrogen, progesterone, cortisol, human chorionic gonadotrophin, and prolactin. These hormones have been proven to work against insulin thereby increasing its resistance [2]. The perinatal nutritional environment is suggested to have a programing effect on an individual's susceptibility to develop obesity [1]. Breastfeeding is suggested to be protective against obesity which could partly be attributable to bioactive compounds present in mature breast milk [3]. However, the specific components of mature breast milk accounting for these effects have not yet been identified. Since the discovery of the adipokines, many strong candidates for the development of metabolic syndrome (Mets) have been proposed [4].

Irisin is a recently discovered myokine which is secreted into the serum by the skeletal muscles post exercise [5,6]. Recent studies also show that low irisin levels are characteristic of and may perhaps be a vital factor contributing towards GDM. Irisin is involved in the conversion of brown to white adipose tissue which not only increase thermogenesis but also improves glucose tolerance, insulin sensitivity, reductions in body weight, decreased fat mass and reduced hepatic triglyceride content [7,8]. Decreased levels of irisin during pregnancy therefore may not only contribute to GDM but also towards obesity owing to poor lipid metabolism. Interestingly, some studies have reported significantly decreased serum irisin levels in GDM

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pregnancies compared to normal pregnancies [9–12], while others have reported little or no difference between the two groups [13–15]. Nevertheless, none fail to acknowledge the risks associated with GDM during and postpregnancy for both the mother and the child.

An important enzyme for the *de novo* lipid synthesis principally expressed in lipogenic tissues is fatty acid synthase (FAS) [16], and it is known to be expressed in placenta [17]. This expression is in turn controlled by "Sterol regulatory element-binding proteins-1c" (SREBP1c) levels. It is observed that whenever there are a decreased cellular sterols and/or polyunsaturated fatty acid level; there is increase FAS gene transcription *via* actions of SREBP-1c. Expression of SREBP-1c is controlled by circulating hormones and nutrients within the body [18]. Recent reports reveal that in type II diabetes; the expression of SREBP-1c is decreased as a consequence of impaired insulin signaling. This will in turn cause irregular lipid synthesis especially during pregnancy.

However, whether these biomarkers remain elevated post-partum and released in mature breast milk to cause a continuous supply for the baby remains to be identified. Therefore, through this study we aim to estimate the levels of irisin and SREBP-1c during pregnancy and in mature breast milk in lactating women with and without GDM and relate them with maternal lipid profile and weight gain of the newborn babies.

Materials and methods

This study recruited 66 pregnant women between the ages of 20 and 35 years who visited the outpatient clinic from July 2016 to August 2017 at the Taj Medical Centre and Aga Khan University, Karachi. All study subjects underwent an oral glucose tolerance test at 24–28 weeks of gestation and were classified as GDM ($n = 33$) or normal glucose tolerant women (NGT) ($n = 33$) according to the International Association of the Diabetes and Pregnancy Study (IADPSG) guidelines [19]. The pregnant females were followed up from 24–28 weeks of gestation till 6 weeks' postdelivery. Pregnant subjects with preexisting diabetes, hypertension, twin pregnancies, and assisted pregnancies were excluded from this study. After receiving ethical approval from the institutional ethical review board (Ref No. 4211-BBS-ERC-16) and written and informed consent from all subjects, 5 ml of maternal blood samples were collected twice; first at 28th week of gestation and again at 6 weeks post-partum.

Similarly, two breast milk samples of the lactating mothers were collected; one within 72 hours of birth (colostrum =3 ml) and second at 6 weeks post-partum (mature milk =10 ml) with a manual breast pump. The mothers were instructed to refrain from feeding for at least 2 hours (8 am till 10 am) before collecting the sample. These samples were aliquoted and were stored in the dark at −80 °C until analysis. For biomarker analysis, milk samples were pretreated according to an established protocol [20]. Briefly, after thawing at room temperature the samples were vortexed and sonicated three times for a 5-s burst. This was followed by preparing skim milk by centrifugation of whole milk at 14,000 rpm, for 30 minutes at 4 °C. The resulting translucent sample was used for analysis. All assays were carried out within 2 months of storage. Irisin and SREBP-1c levels were analyzed by commercially available ELISA kit (Kit Cat number 95512 and F9350, Glory Science Co Ltd).

Additionally, a spike-and-recovery experiment was designed to assess the difference in assay response according to a set protocol [21]. Briefly, the following procedure and samples were used (i) sample diluent serving as blank, (ii) sample diluent spiked with known concentration of standard (to allow quantification of exogenous analyte), (iii) Two breast milk analytes without spiking (to allow quantification of endogenous analyte), (iv) Two breast milk analytes spiked with known concentration of standard (to allow quantification of both exogenous and endogenous analyte). Ten microliters of spike stock solution was added to the samples, calculated to yield 240 pg/ml spike concentration. Values used for breast milk spiked samples reflect subtraction of the endogenous (no-spike) sample value. The samples were run in duplicates and a mean score was used. The recovery rate for all samples was between 93 and 98% with intra-assay and interassay coefficients of variation <10% and <15%, respectively. A range between 80 and 120% recovery is considered acceptable for such experiments [22].

Weight of mothers was assessed at the time of first visit (i.e. 12–15 weeks of gestation), at the time of glucose tolerance test, i.e. 28 weeks of gestation and at 6 weeks' post-partum. Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). South Asian reference range for BMI was used to categorize study subjects [23]. Clinical data including maternal age, height, family history of diabetes mellitus, gender, and weight of newborn were recorded from the patient record card.

Statistical analysis

Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS

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version 21; IBM Corp Inc, Armonk, NY, USA). Descriptive analysis of categorical data was presented in terms of frequencies and percentages, whereas that for continuous variables was expressed as mean ± standard deviation. Continuous variables were assessed by Mann–Whitney U test. Spearman's correlation between serum irisin, SREBP-1c and clinical parameters were also calculated. p value $<.05$ were regarded to be significant.

Results

The results are displayed in Tables 1–2. The study subjects were aged matched therefore we did not find any difference. Females with GDM had a higher body weight, fasting blood glucose (FBG), and random blood glucose (RBG) at 6 weeks postpartum ($p < .01$). Interestingly, the HbA1c levels at follow up were within normal range for the GDM subjects. The newborn data showed that babies of GDM positive mothers had a higher weight by scan at 28 weeks of gestation, at birth and at follow up 6 weeks after birth (Table 1).

Table 2 shows the biomarker levels in the study subjects. We observed a low serum irisin level in GDM females at 28, 6 weeks postpartum compared to normo-glycemic females ($p < .01$). Similarly, colostrum and mature breast milk irisin was also low in GDM subjects. SREBP1-c profile showed a similar trend of low serum levels in GDM, however, these levels reduced from a very low value to undetectable range in colostrum and mature breast milk respectively. However, we found no differences in the lipid profile post pregnancy in the study cohort. Furthermore, we found weak to moderate correlations of Serum irisin with BMI ($r = 0.439$; $p > .001$) GTT 0 hours ($r = 0.403$; $p = .01$), HbA1c ($r = -0.312$; $r = .011$), FBG ($r = 0.992$; $p = .008$) and baby weight at birth ($r = 0.486$; $p < .001$). Colostrum and mature breast milk irisin showed positive associations with baby weight at 6 weeks ($r = 0.325$; $p = .017$; $r = 0.296$; $p = .022$, respectively). Serum SREBP-1c at 6 weeks correlated with ~~the baby weight at 6 weeks ($r = 0.255$; $p = .039$),~~ RBG at 6 weeks ($r = 0.318$; $p = .009$), and HbA1c ($r = -0.292$; $p = .011$). However all correlations were lost once we adjusted for maternal BMI. Therefore, these associations were dependent on the maternal weight and BMI.

Discussion

The finding of our study showed lower levels of irisin in serum, colostrum and mature breast milk of GDM females. These low levels may increase the risk of developing diabetes mellitus type 2, hypoglycaemia, and respiratory distress syndrome [10,11]. Contrary to our finding, one study found irisin levels to increase from colostrum to transitional and mature milk in both normal glucose tolerant and GDM patients [10]. Low irisin levels in the serum, mature breast milk and colostrum acts as a continued stressor from fetal to infant life. This may continue to have adverse effects on the baby's health and lipid regulation as long as breast-feeding is continued. Irisin has proven to play a vital role in improving obesity and glucose homeostasis. It has been proposed that irisin increases adenosine monophosphate (AMP) activated protein kinase phosphorylation and increases glucose uptake; therefore plays an important role in glucose metabolism [24]. Irisin further has proven to inhibit atherosclerosis by endothelial proliferation [25], cholesterol synthesis in the hepatocytes [26] and promote osteoblast proliferation and differentiation [27]. Therefore, we believe that low irisin in the GDM population may have crucial effects on the mother's and baby's health, both during pregnancy and post-partum. It is also postulated that

Table 1. Maternal and newborn data.

Variables	NGT $n = 33$ Mean ± SD	GDM $n = 33$ Mean ± SD	p value
Maternal data			
Age (year)	24.10 ± 1.77	24.23 ± 1.14	.412
BMI (kg/m^2)	20.55 ± 3.76	25.22 ± 4.24*	<.001
GTT at 0 hours	78.24 ± 12.05	103.27 ± 15.15	<.001
GTT at 2 hours	120.48 ± 10.47	162.66 ± 44.68	<.001
RBG −6 weeks postpartum (mg/dl)	107.04 ± 19.45	144.00 ± 3.66*	<.001
HbA1c −6 weeks post-partum (mg/dl)	NA	5.23 ± 0.92	–
New-born data			
Abdominal circumference by scan (cm) at 28 weeks of gestation	26.80 ± 3.98	28.51 ± 5.09	.135
Foetal weight by scan (kg) at 28 weeks of gestation	1.98 ± 0.54	2.28 ± 0.59	.008
Baby gender	Male 19 (57.57) Female 14 (42.42)	Male 16 (48.48) Female 17 (51.51)	.547
Baby weight at birth (kg)	3.53 ± 0.51	4.41 ± 0.97	<.001
Baby weight at 6 weeks (kg)	4.35 ± 0.40	5.53 ± 0.15*	<.001

BMI: body mass index; RBG: random blood glucose. Values expressed as mean and standard deviation and absolute number with percentage in parenthesis.

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Table 2. Maternal serum, colostrum, and mature breast milk biomarker data.

Variables	NGT $n = 33$ Mean ± SD	GDM $n = 33$ Mean ± SD	p Value
Irisin profile			
Serum Irisin at 28-week gestation (pg/ml)	72.94 ± 9.11	42.09 ± 3.21	.01
Serum Irisin at 6 weeks post-partum (pg/ml)	264.97 ± 40.88	138.32 ± 6.82	.003
Colostrum Irisin (pg/ml)	57.08 ± 8.28	10.36 ± 4.73	<.001
Mature breast milk Irisin (pg/ml)	56.40 ± 9.55	15.35 ± 0.42	<.001
SREBP-1c profile			
Serum SREBP1-c at 28-week gestation (pg/ml)	73.94 ± 9.41	43.62 ± 7.33	.013
Serum SREBP1-c at 6 post-partum (pg/ml)	38.33 ± 1.752	20.92 ± 1.755	< .001
Colostrum SREBP1-c (pg/ml)	9.39 ± 4.07	4.09 ± 1.65	.233
Mature breast milk SREBP1-c (pg/ml)	0.00	0.00	–
Lipid profile at 6 weeks post-partum			
Cholesterol (mg/dl)	187.66 ± 31.50	172.84 ± 44.03	.518
TAG (mg/dl)	133.09 ± 17.97	147. ± 11.00	.340
HDL (mg/dl)	45.72 ± 9.40	47.66 ± 8.20	.612
LDL (mg/dl)	107.56 ± 3.69	113.73 ± 5.10	.584

Values expressed as mean and standard deviation.

the levels affect intrauterine growth of the fetus. However recent studies by Briana and group [28] reported that no difference was observed in cord blood levels of intra uterine growth retardation and normal for gestational age babies. Similarly they reported that irisin levels decrease with advancing gestational weeks and this could be attributed to increased maternal fat deposition. That may lead to insulin resistance in the latter half of pregnancy [29]. These findings strongly support our hypothesis and results. As of late, no validated normal range for irisin have been reported, but low serum irisin levels were reported in Japanese population (1.1 ± 0.1 ng/ml for males and 1.2 ± 0.2 ng/ml for females) [30] and in Tehran, Iran (0.81 ± 0.41 ng/ml in normal weight obese and 0.58 ± 0.26 ng/ml controls) [31]. Perhaps these differences in irisin levels are observed due to interpopulation or plasma versus serum sample differences, yet our results are quite similar to the neighboring countries.

Increased levels of FBG/RBG at 6 weeks post-partum were seen in our study. Similar to our findings, a positive association between GDM history, 2-hour glucose; and HbA1c during pregnancy and post-partum diabetes was seen within Chinese women [32]. Interestingly, in a recent study conducted by our group, we found that 14% of GDM positive females developed DM within 2 years of their last pregnancies [33]. Furthermore, we report a higher birth weight as well as infant weight 6 weeks post birth for GDM ~~mothers~~. The incidence of fetal macrosomia ranges between 20 and 40% in GDM positive cases [34], but the baby weight normalizes with time [35]. However, our findings suggests that the constant stress in terms of low irisin though mature breast milk was a trigger for the deranged body fat accumulation and higher body weight of these infants.

We also report a significantly lower level of SREBP-1c in serum and colostrum of GDM positive females however, its level was undetectable in the mature breast milk of both the groups. Further we did not find any differences in maternal lipid profile among the groups. This may be due to the fact that GDM increases concentration of inflammatory cytokines which induces fatty acid synthase (FAS) expression but not the expression of SREBP protein [36]. A study found significant increase in expression of SREBP-2 and fatty acid synthase (FAS) in the placenta while both 3-hydroxy-3-methylglutaryl-CoA (HMG Co-A) lyase and SREBP-1 were not modified. Supposedly, in GDM as irisin levels tend to decrease, insulin resistance tend to increase which in turn may effect levels of SREBP-1 [37]. Since SREBP proteins are responsible for uptake and synthesis of fatty acids and cholesterol [38], our hypothesis suggested that there should be higher levels of lipid biomarkers in the maternal serum. Yet, no significant difference was observed in the lipid profile of GDM and non-GDM mothers. We assume that since the GDM inflicted mothers were kept on diet and drug regimens, that may have contributed to the within normal range levels as seen.

Lastly, we report a weak to moderate correlation of irisin with maternal BMI, GTT, baby weight at birth, and FBG. In addition, colostrum and mature breast milk irisin showed positive associations with baby weight at 6 weeks. However, all correlations were lost once we adjusted for maternal BMI. Therefore, we believe that these associations were dependent on the maternal weight and BMI. A similar finding was reported that irisin was positively related with BMI and FBG [39], yet another study reported that none of the anthropometric parameters to correlate with serum irisin levels [40]. Another study's findings suggested that irisin was negatively correlated with age and FBG while positively

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correlated with HDL-c [41]. Interestingly, Sinanoglu and group [40] proposed an ethnicity and maternal age related link with the fat content of colostrum instead of the commonly agreed notion of maternal pre pregnancy BMI. They also suggest that this finding can be used to design custom diets for mothers to enhance the mature breast milk nutritional value and in turn have a positive impact on new born health. Furthermore, another recent study measured irisin levels in babies and compared them with growth rate and insulin levels. They report that low irisin levels were seen in intra uterine growth restricted babies and irisin showed a weak positive correlation with the birth weight of babies. In addition, a weak positive association was also seen for fetal irisin and insulin concentrations [42].

We postulate that derangement of both irisin and SREBP in pregnancy may ~~be~~ trigger abnormal fatty acid (FA) metabolism. Furthermore, impaired metabolism causes accumulation of reactive lipid species eventually altering the response to tissue insulin signaling. Irisin may induce gene expression changes by directly acting on the tissues or indirectly by inducing a "factor X". This has significant implication for irisin as a novel therapeutic target. However, further mechanistic research is required to validate and propose this effect.

Furthermore, in addition to being secreted from skeletal and cardiac muscle, irisin has also been detected in the brain (neurons and neuroglia), the skin (sebaceous glands), the testis, epididymis, liver, pancreas, spleen, stomach, and three major paired salivary glands (submandibular, sublingual, and parotid) [43–45]. It is removed from the body mainly through the hepato-biliary system and the kidneys [45–47]. It is possible that these molecules may act as trophic or mediating agents that sends signal to brain, gut, muscle, and adipose tissue during pregnancy or *via* breast milk post-partum. Therefore, it is plausible to comment that irisin may modulate energy expenditure or food intake through topical, paracrine or autocrine actions. This could potentially have postnatal effects on the baby *via* skin, tongue or gut to modify energy metabolism and stimulate appetite center in brain, tissue hyperplasia or hypertrophy in adipose tissue and liver [48–50]. The exact focal mechanism or function however is currently unknown, so future *in vivo* studies are required that might provide the conclusive results to consolidate this hypothesis.

Conclusions

Low irisin and SREBP-1c levels in the serum, mature breast milk and colostrum may favor development of GDM in pregnant subjects. Further, low mature breast milk irisin ~~and SREBP-1c~~ levels may act as a continued stressor from fetal to infant life till breast-feeding is continued. Further studies are required to identify the mechanistic relationship between these biomarkers and GDM.

Disclosure statement

The authors declare that they have no conflict of interest.

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