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Vitamin D Supplementation Reduces Serum Chemerin Level in Gestational Diabetes Mellitus Rat Model

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is the most common metabolic disorder that increases the prenatal morbidity. Data regarding the association between circulating chemerin level and GDM remains controversial. On the other hand, Vitamin D deficiency is common in pregnancy and may increase the frequency of GDM.

Aim of Study: This study was conducted to examine the effects of Vitamin D_3 supplementation on serum chemerin level and some metabolic parameters in GDM rat model.

Material and Methods: Healthy female white albino rats were divided randomly into three groups (n=10 rats): Group I (normal pregnant group); fed on normal diet for five weeks before induction of pregnancy. Group II (GDM-induced); fed High Fat-Sucrose Diet (HFSD) for five weeks before induction of pregnancy then injected Intraperitoneally (I.P) by Streptozotocin (STZ) (25mg/kg) on the 7^{th} day of gestation. Group III (GDM-induced group supplemented with Vitamin D_3); GDM-induced as before and injected Intramuscularly (I.M) with 20,000IU/kg of cholecalciferol on days 1 and 14 of gestation. On the 19^{th} day of gestation, serum chemerin, estradiol, progesterone, glucose, insulin and Insulin Resistance index (HOMA-IR), Total Cholesterol (TC), Triglycerides (TG), Low Density Lipoprotein-cholesterol (LDL-c), High Density Lipoprotein-cholesterol (HDL-c), Very Low Density Lipoprotein-cholesterol (VLDL-c), Tumor Necrosis Factor alpha (TNF a) and Malondialdehyde (MDA) levels and Serum Superoxide Dismutase (SOD) activity were estimated for all groups.

Results: GDM-induced rats showed significantly increased serum glucose, HOMA-IR, TG, TC, LDL-c, VLDL-c, MDA, and TNF a levels while showed significantly decreased serum insulin and HDL-c levels and SOD activity when compared to normal pregnant control rats. GDM-induced rats also showed significantly increased serum chemerin levels that showed significant positive correlations with serum glucose, insulin, HOMA-IR, TG, TC, LDL-c, VLDL-c, MDA, and TNF a levels but showed significant negative correlations with serum HDL-c level and SOD activity. Noteworthy, Vitamin D_3 administration significantly improved these parameters in GDM-induced group supplemented with Vitamin D_3.

Conclusion: Our results denoted the protective effect of Vitamin D_3 supplementation on GDM that may be through improving the antioxidant and inflammatory status. Decreasing circulating chemerin level may play a role in this protective effect.

Key Words: *Chemerin – Gestational diabetes mellitus – Pregnancy – Vitamin D.*

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Introduction

GESTATIONAL Diabetes Mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy in patients with no history of diabetes prior to gestation. It is associated with an increased risk of pregnancy complications for both mother and foetus **[1]**.

The pathophysiologic mechanism of GDM is similar to Type 2 Diabetes Mellitus (T2DM), including insulin resistance, oxidative stress and systemic inflammation **[2]**. Many of these maternal metabolic changes during gestation are influenced by different adipokines produced in the placenta and adipose tissue **[3]**.

Chemerin is a novel cytokine secreted mainly from white adipose tissues and was initially considered as a chemotactic factor generated in inflammatory conditions, but more recently, it is considered as an adipokine regulating metabolism and energy balance **[4]**. It has been implicated as an independent predictor of T2DM and increased chemerin levels were associated with inflammation and metabolic syndrome even after adjustment of waist circumference **[5]**. It has also been suggested that chemerin may play an important role in the

pathogenesis of GDM, however, studies on the association between circulating chemerin level and GDM yielded inconsistent findings and remained controversial [6-8].

On another note, non-skeletal functions of Vitamin D has received tremendous attention with increasing number of reports of association between Vitamin D deficiency and several health problems such as hypertension, cancer, cardiovascular diseases, and diabetes mellitus [9].

Studies have also shown increased prevalence of Vitamin D deficiency in pregnancy [10,11]; however, conflicting evidence exists to whether low levels of 25-hydroxyVitamin D are associated with increased risk of GDM [12,13].

Furthermore, data remain limited whether supplementation with Vitamin D will prevent GDM or improve glucose tolerance in GDM [14]. While Shahgheibi et al., [15] reported the effectiveness of Vitamin D supplementation in reducing GDM and controlling blood glucose, Tehrani et al., [16] revealed that Vitamin D supplementation had no effect on the incidence of GDM during pregnancy.

Therefore, this study aimed to investigate the effects of Vitamin D_3 supplementation on GDM and the possible implication of circulating chemerin level.

Material and Methods

This study was conducted in Faculty of Medicine, Zagazig University in the period from January to April 2019 and involved 45 healthy albino rats (40 virgin females weighing 113-137gm, 50 day old and 5 adult males for fertilization weighing 190-216gm), were obtained from the Animal House of Faculty of Veterinary Medicine, Zagazig University. Rats were kept in steel wire cages under hygienic conditions and fed the commercial normal rodent chow, but the rats in GDM groups received High Fatty-Sucrose Diet (HFSD) with free access to water and kept at room temperature on a 12h light/dark cycle. The animal experiments were approved by the Institutional Research Board.

Induction of pregnancy: Rats were examined for estrous cycles for 2 consecutive weeks. Every morning, vaginal secretion was taken from each rat by inserting a plastic pipette containing 1ml of normal saline (NaCl 0.9%) into the rat's vagina and flushing the cells from the vaginal lining. One or two drops of vaginal secretion were placed on a separate clean glass slide. Unstained vaginal secretions were directly viewed under a light microscope at 40x magnification. Rats follow a 4-day pattern of estrous cycle; proestrous (showing round nucleated epithelial cells in the vaginal smear), estrous stage (with cornified or irregular shape of epithelial cells in the vaginal smear), metaestrous (with low number of round cells), and diestrous stage (with mostly small and round cells). After five weeks of dietary manipulation, rats in estrous stage were allowed to mate with a mature male rat in a separate cage. After mating, female rats were subsequently isolated until confirming copulation in the next morning by the presence of a copulation plug or spermatozoa in the vaginal smear. The presence of sperms indicates the first day of gestation [17]. Four rats from the forty not get pregnant and excluded from the study.

36 pregnant rats were randomly assigned to three groups: Group I (normal pregnant control group) (n=10): Pregnant female albino rats fed on normal diet (25.8% protein, 62.8% carbohydrates and 11.4% fat) for five weeks before induction of pregnancy then has been injected with citrate buffer Intraperitoneally (I.P) on the 7 th day of gestation [18]. Group II (GDM-induced group) (n=13) rats were fed with High Fatty-Sucrose Diet (HFSD) (25% sucrose, 40% beef tallow and 20% casein protein-HFSD was prepared in the Department of Nutrition, Faculty of Veterinary Medicine, Zagazig University) for five weeks before induction of pregnancy then rats received a single dose of Streptozotocin (STZ) (Sigma Aldrich Co.-USA) on the 7 th day of gestation [18]. Group III (GDM-induced group received Vitamin D (n=13) GDM-induced as mentioned above then rats were injected I.M. with 20,000IU/kg of cholecalciferol (Devarol -S-200.000I.U. 1AMP 2ml, Memphis Co. for Pharm. & Chem. Ind. (MEMCO)-Egypt) on Days 1 and 14 of gestation while the other groups received sesame oil (Sigma Aldrich Co.-USA) as placebo [19,20]. No rats died after STZ injection, and the statistical analysis was done concerning 10 rats from each group).

Induction of experimental GDM: On the 7 th day of pregnancy HFSD-fed rats were fasted for 16 hours and then were injected I.P. with a low dose of STZ (25mg/kg) (Sigma Aldrich, U.S.A.) dissolved in 0.1mol/L sodium citrate (PH 4.5) [18]. The rats were provided with oral 10% glucose solution after 6 hours of STZ administration for the next 48 hours. After 72 hours, fasting blood glucose level was measured using glucometer

(ACCU CHEK, Rhoche Diagnostics, Germany) and rats with blood glucose levels above 250mg/dl were considered as DM model rats [21]. All rats were continued on same diet until end of experiment.

Sample collection:

Blood samples were collected at the end of experiments (19th day of pregnancy) after overnight fasting from retro orbital venous plexus, and serum was separated by centrifugation of blood at 3000 rpm for 20 minutes and kept at (–20ºC) until used.

Serum analysis:

- *Serum chemerin:* Was measured as described by Tan et al., [22] using rat ELISA kit (kitsrom Uscn Life Science, USA).
- *Measurement of serum glucose, insulin and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR):* Serum glucose was estimated according to the method of Tietz [23] using specific glucose kit (Bioscience, Egypt).

Insulin was measured according to Temple et al., [24] using specific insulin kit (BioSource Belgium).

HOMA-IR was calculated by using the following formula:

$$\text{HOMA-IR} = \frac{\text{Insulin (}\mu\text{IU/mL) X glucose (mg/dl)}}{405} \quad [25]$$

- *Measurement of serum lipids:* TC and TG were measured by enzymatic colorimetric method by using specific cholesterol and triglycerides kits (Spinreact Spain) according to Tietz [23]. HDL-c was measured by precipitating reagent method using HDL-c precipitating reagent kit (Spinreact, Spain) according to Tietz [23]. LDL-c and VLDL-c were measured by using Friedewald et al., [26] formula.

$$\text{LDLc} = \text{TC} - \text{HDLc} - \left(\frac{\text{TG}}{5}\right) \quad \text{VLDLc} = \frac{\text{TG}}{5}$$

- *Measurement of serum estradiol and progesterone levels:* Serum estradiol and progesterone levels were measured using rat estradiol and progesterone ELISA kits respectively (Shanghai Sunred Biological Technology, China) as described by Tietz [23].
- *Serum TNF-α level:* Was measured using specific ELISA kit (Sigma-Aldrich Co., USA) according to Fernando et al., [27].
- *Serum MDA level:* Was measured using MDA Assay Kit (Sigma Aldrich Co., USA) according to Satoh [28].
- *Serum SOD activity:* Was measured using specific kit (Sigma Aldrich Co., USA) according to Nishikimi et al., [29].

Statistical analysis:

Data were presented as mean ± SD. SPSS Version 18.0 (SPSS Inc., Chicago, IL, United States) was used for performing the statistical analysis. Analysis of Variance (ANOVA) followed by LSD post hoc test was performed to compare means of the different groups. Pearson's correlation analysis was performed to detect correlations between serum chemerin and the measured parameters. p-value <0.05 was considered to be statistically significant for all statistical tests done.

Results

In GDM group, rats exhibited significant increase in serum chemerin (p<0.001), glucose (p <0.001), HOMA-IR (p<0.001), TC (p<0.001), TG (p<0.001), LDL-c (p<0.001), VLDL-c (p<0.001), MDA (p<0.001), and TNF α (p<0.001), while they showed significantly decreased serum insulin (p<0.001), HDL-C (p<0.001) and SOD activity (p<0.001) when compared to normal pregnant group. In addition, there were no significant differences in serum estradiol or progesterone (p>0.05) in GDM group when compared to normal pregnant group (Table 1).

However, it was found that Vitamin D3 supplementation in GDM supplemented with Vitamin D group significantly decreased serum chemerin (p<0.001), glucose (p<0.001), HOMA-R (p<0.001), TC (p<0.001), TG (p<0.001), LDL-c (p<0.001), VLDL-c (p<0.001), MDA (p<0.001), and TNF α (p<0.001), but significantly increased serum insulin (p<0.01), HDL-C (p<0.01) and SOD activity (p <0.001) with no effect on serum estradiol or progesterone (p>0.05) levels when compared to GDM non supplemented with Vitamin D group (Table 1).

Moreover, serum chemerin levels showed significant positive correlations with serum glucose, insulin, HOMA-IR, TC, TG, LDL-c, VLDL-c, MDA, and TNF α levels but showed significant negative correlations with serum HDL-c level and SOD activity and didn't correlate to serum estradiol or progesterone in both GDM and GDM + Vitamin D3 groups (Table 2) and Figs. (1-26).

Table (1): Serum levels of all parameters in the three studied groups.

Groups / Parameters	Group I	Group II	Group III
Chemerin (Pg/ml):			
X ± SD	16.9±1.45	51.91±6.26	28.53±2.93
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
Glucose (mg/dL):			
X ± SD	88.71±7.64	268.39±10.77	171.40±14.01
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
Insulin (uIU/mL):			
X ± SD	22.89±1.33	14.56±2.02	17.261±1.54
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a**
			p<0.01 **b**
HOMA-IR:			
X ± SD	5.0±0.42	9.68±1.58	7.34±1.18
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
TC (mg/dL):			
X ± SD	120.27±3.80	157.38±10.61	133.17±6.12
p-value of LSD		*p*<0.001 **a**	*p*<0.01 **a**
			p<0.001 **b**
TG (mg/dL):			
X ± SD	49.77±7.03	163.46±6.90	99.68±9.87
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
HDL-c (mg/dL):			
X ± SD	46.68±3.42	33.20±3.63	41.07±2.8
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a**
			p<0.01 **b**
LDL-c (mg/dL):			
X ± SD	63.62±6.79	91.4864±12.38	72.16±6.83
p-value of LSD		*p*<0.001 **a**	*p*<0.05 **a**
			p<0.001 **b**
VLDL-c (mg/dL):			
X ± SD	9.95±1.40	32.69±1.38	19.93±1.97
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
Estradiol (pg/ml):			
X ± SD	96.78±7.38	92.48±7.16	94.03±8.37
p-value of LSD		*p*>0.05 **a**	*p*>0.05 **a,b**
Progesterone (pg/ml):			
X ± SD	59.96±3.30	58.32±3.69	58.48±3.78
p-value of LSD		*p*>0.05 **a**	*p*>0.05 **a,b**
TNF-α (pg/ml):			
X ± SD	30.82±2.01	54.95±4.00	3 8.94±3.01
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
MDA (nmol/ml):			
X ± SD	42.30±2.88	61.18±5.52	49.73±3.28
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**
SOD (U/L):			
X ± SD	52.91±2.94	34.17±3.38	42.54±3.41
p-value of LSD		*p*<0.001 **a**	*p*<0.001 **a,b**

a = Significant Versus Group I.
b = Significant versus Group II.

Table (2): Pearson's correlation analysis between serum chemerin and all parameters in Group II (GDM) and Group III (GDM supplemented with Vitamin D3).

Groups / Parameters	Group II	Group III
Glucose	*r*=0.903, *p*<0.001	*r*=0.950, *p*<0.001
Insulin	*r*=0.702, *p*<0.05	*r*=0.785, *p*<0.01
HOMA-IR	*r*=0.812, *p*<0.01	*r*=0.905, *p*<0.001
TC	*r*=0.884, *p*<0.001	*r*=0.780, *p*<0.01
TG	*r*=0.916, *p*<0.001	*r*=0.908, *p*<0.001
HDL-c	*r*=–0.812, *p*<0.01	*r*=–0.924, *p*<0.01
LDL-c	*r*=0.894, *p*<0.001	*r*=0.819, *p*<0.01
VLDL-c	*r*=0.916, *p*<0.001	*r*=0.908, *p*<0.001
Estradiol	*r*=–0.321, *p*>0.05	*r*=–0.176, *p*>0.05
Progesterone	*r*=–0.401, *p*>0.05	*r*=–0.226, *p*>0.05
TNF-α	*r*=0.923, *p*<0.001	*r*=0.865, *p*<0.01
MDA	*r*=0.785, *p*<0.01	*r*=0.748, *p*<0.05
SOD	*r*=–0.783, *p*<0.01	*r*=–0.801, *p*<0.01

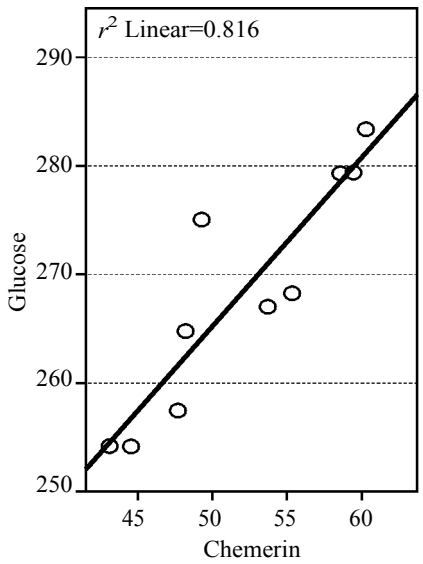

Fig. (1): Correlation between serum chemerin and glucose level in GDM (Group II).

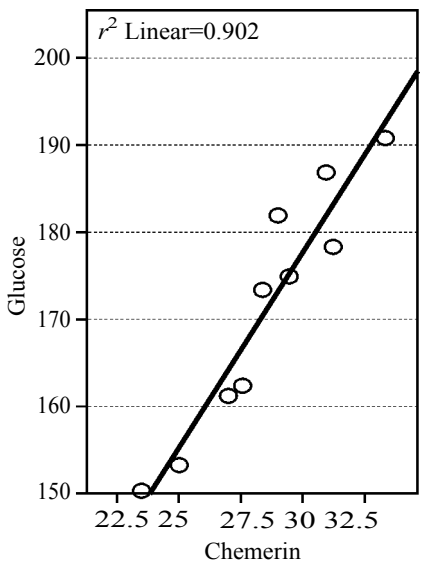

Fig. (2): Correlation between serum chemerin and glucose level in GDM + Vitamin D3 (Group III).

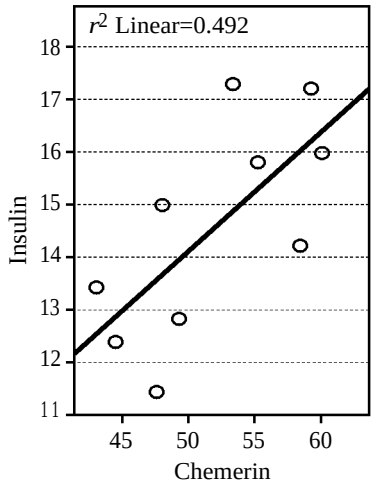

Fig. (3): Correlation between serum chemerin and insulin levels in GDM (Group II).

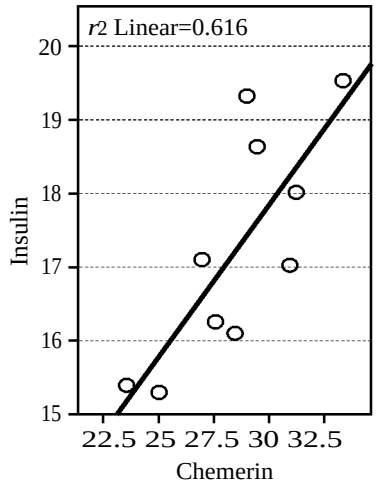

Fig. (4): Correlation between serum che-merin and insulin levels in GDM + Vitamin D_3 (Group III).

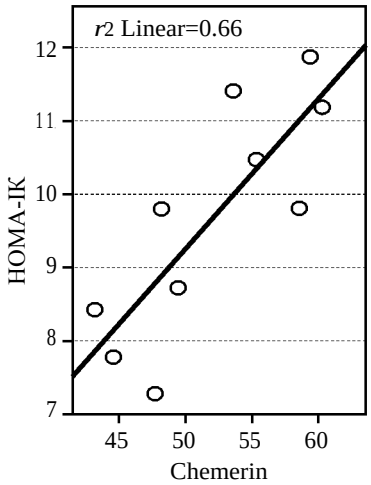

Fig. (5): Correlation between serum chemerin and HOMA-IR in GDM (Group II).

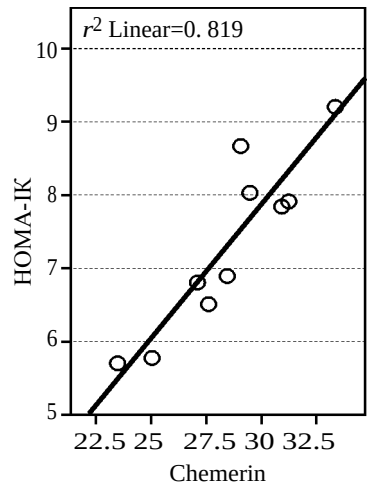

Fig. (6): Correlation between serum chemerin and HOMA-IR in GDM + Vitamin D_3 (Group III).

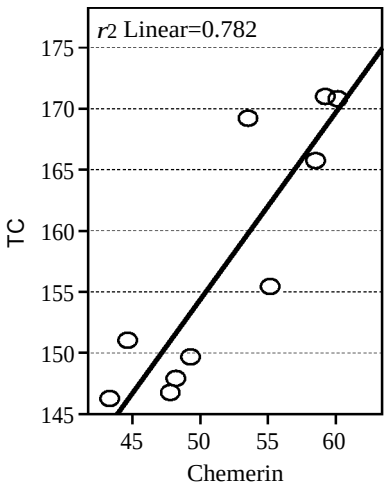

Fig. (7): Correlation between serum chemerin and TC in GDM (Group II).

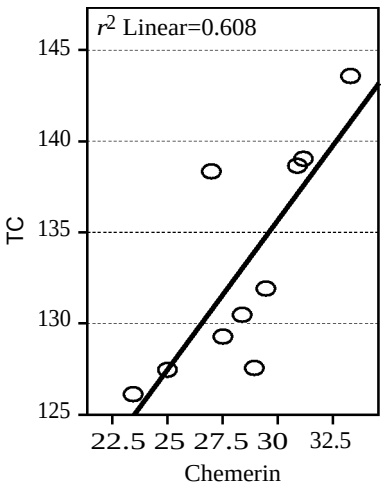

Fig. (8): Correlation between serum chemerin and TC in GDM + Vitamin D_3 (Group III).

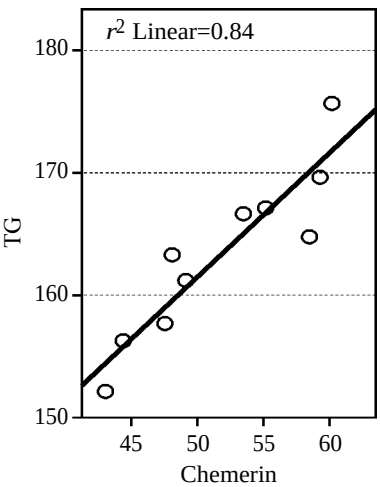

Fig. (9): Correlation between serum chemerin and TG in GDM (Group II).

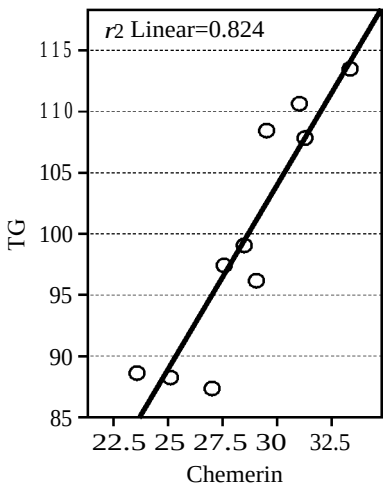

Fig. (10): Correlation between serum chemerin and TG in GDM + Vitamin D_3 (Group III).

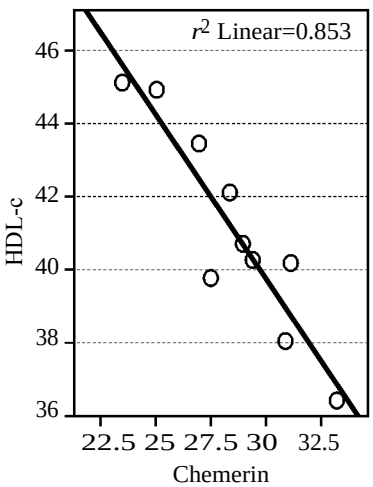

Fig. (11): Correlation between serum chemerin and HDL-c in GDM (Group II).

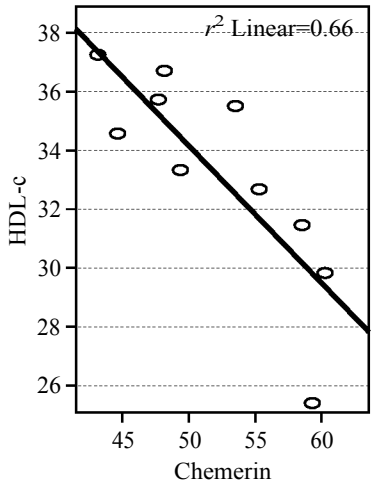

Fig. (12): Correlation between serum chemerin and HDL-c in GDM + Vitamin D3 (Group III).

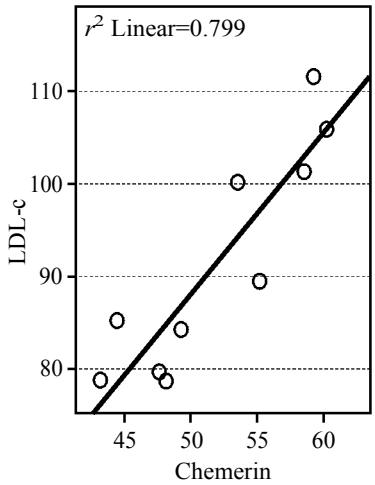

Fig. (13): Correlation between serum chemerin and LDL-c in GDM (Group II).

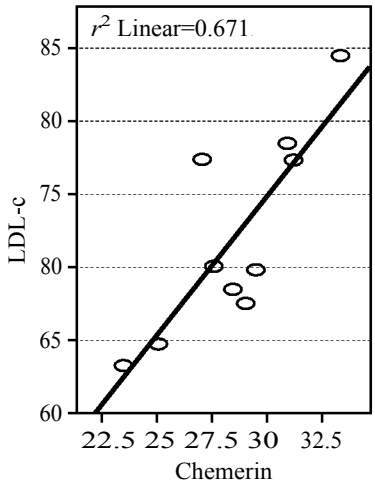

Fig. (14): Correlation between serum chemerin and LDL-c in GDM + Vitamin D3 (Group III).

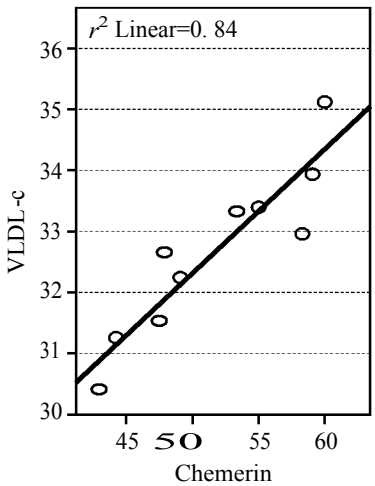

Fig. (15): Correlation between serum chemerin and VLDL-c in GDM (Group II).

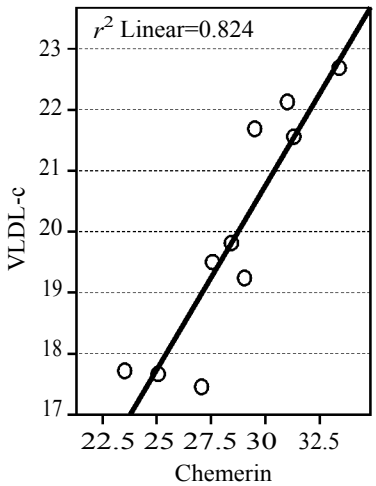

Fig. (16): Correlation between serum chemerin and VLDL-c in GDM + Vitamin D3 (Group III).

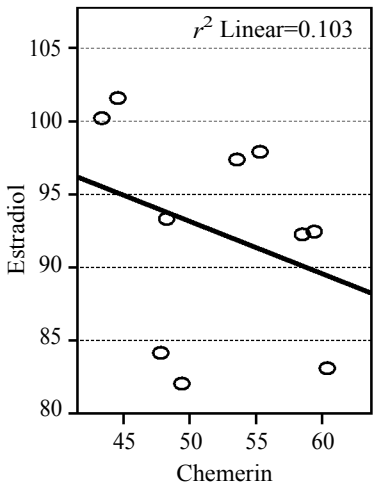

Fig. (17): Correlation between serum chemerin and estradiol in in GDM (Group II).

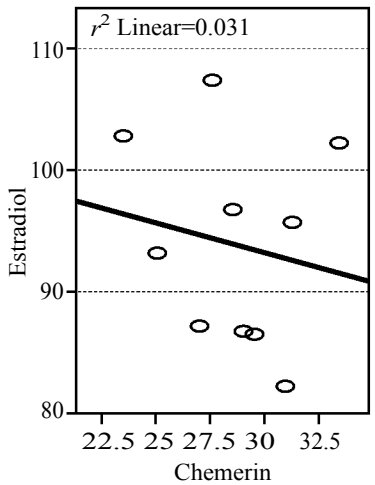

Fig. (18): Correlation between serum chemerin and estradiol in GDM + Vitamin D3 (Group III).

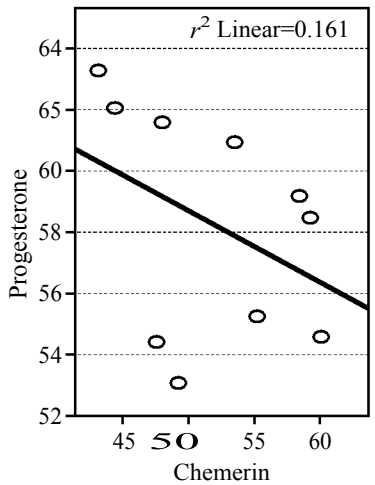

Fig. (19): Correlation between serum chemerin and progesterone in GDM (Group II).

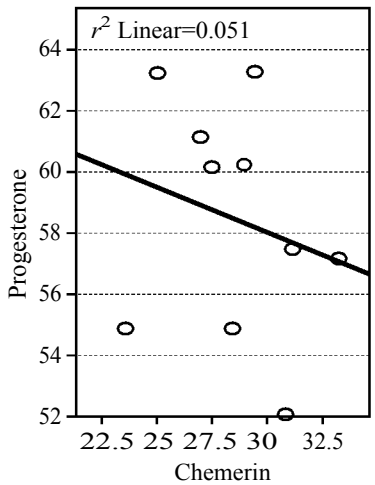

Fig. (20): Correlation between serum chemerin and progesterone in GDM + Vitamin D3 (Group III).

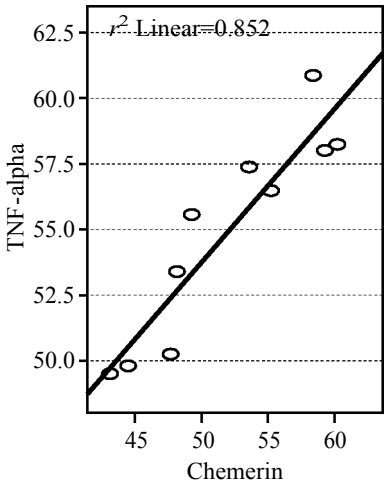

Fig. (21): Correlation between serum chemerin and TNF-a in in GDM (Group II).

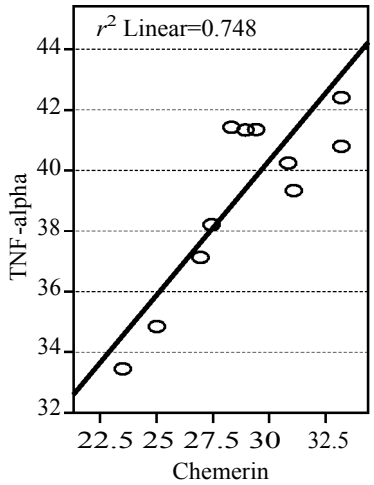

Fig. (22): Correlation between serum chemerin and TNF-a in GDM + Vitamin D3 (Group III).

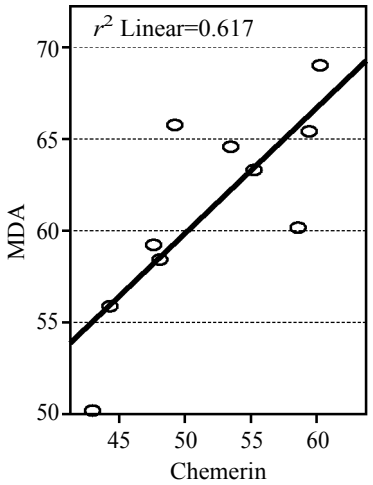

Fig. (23): Correlation between serum chemerin and MDA in in GDM (Group II).

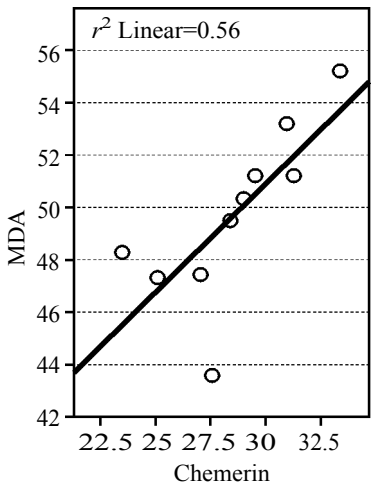

Fig. (24): Correlation between serum chemerin and MDA in GDM + Vitamin D3 (Group III).

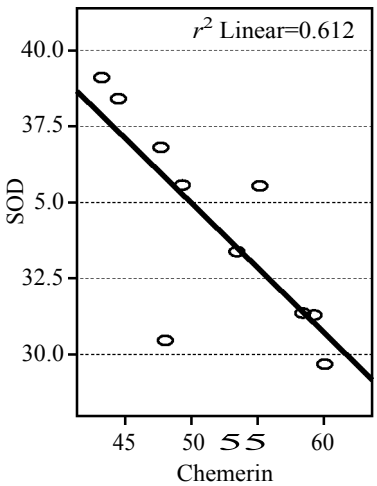

Fig. (25): Correlation between serum chemerin and SOD in in GDM (Group II).

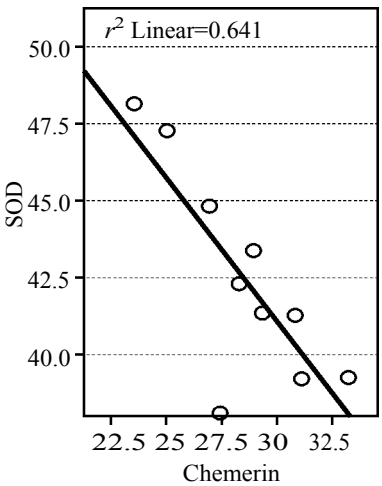

Fig. (26): Correlation between serum chemerin and SOD in GDM + Vitamin D3 (Group III).

Discussion

The prevalence of GDM is increasing rapidly worldwide along with the changes in lifestyle and increasing incidence of obesity and older age of pregnant women [30]. Similar to Type 2 Diabetes Mellitus (T2DM), the changes of adipokine and cytokine production were also detected during GDM development and progression [31]. One of these adipokines is chemerin, which is increased in obesity and T2DM [32].

Sufficient levels of Vitamin D can also be effective in controlling blood glucose in pregnant women [33].

Thus, we aimed in this study to examine the effects of Vitamin D3 supplementation on GDM and try to identify the possible mechanisms of action in relation to serum chemerin level.

In the present study, serum glucose level was higher in GDM group compared to control group, confirming the hyperglycemic state of rats. GDM group also showed significantly decreased serum insulin with increased HOMA-IR index compared to the control group. These results indicate Insulin Resistance (IR). If beta cells are not able to compensate for the increase in insulin resistance, this can lead to GDM [34]. It is thought that IR is the common pathological process of GDM and T2DM. The increase of IR is more common in the late stage of pregnancy of GDM women [35].

Whereas, Vitamin D supplementation significantly increased serum insulin and decreased hy-

perglycemia and HOMA-IR index in the treated GDM group when compared to the untreated one. In agreement with our findings, Shahgheibi et al., [15] also reported the protective effect of Vitamin D_3 supplementation in reducing gestational diabetes for high-risk pregnant women.

Vitamin D is engaged in regulation of Ca^{2+} influx to pancreatic β cells. It activates Protein Kinase A (PKA) that phosphorylates different proteins involved in L-type voltage-dependent Ca^{2+} channels related increase of insulin secretion. It also activates Phospholipase C (PLC) with Inositol 3 Phosphate (IP_3) (which contributes to the release of Ca^{2+} from endoplasmic reticulum) and Diacyloglycerol (DAG) synthesis (that in turn activates Protein Kinase C (PKC); responsible for phosphorylation of the ATP-sensitive potassium channels and L-type voltage-dependent Ca^{2+} channels). All of these processes stimulate secretion of insulin [36]. Moreover, it has been reported that Vitamin D_3 treatment reversed the high glucose-induced β-cell apoptosis [37].

Vitamin D is also involved in regulating insulin sensitivity by stimulating the expression of insulin receptors and promoting the expression of Peroxisome Proliferator-Activated Receptor (PPAR); a nuclear receptor that is involved in fatty acid and glucose metabolism [38]. In addition, Vitamin D appears to enhance the intracellular mechanisms of insulin action mediated by Insulin Receptor Substrate 1 (IRS-1) and up-regulate glucose transporter type 4 (GLUT4) protein expression [39].

Moreover, Hyperdyslipidemia is commonly observed in GDM [40]. This finding was also observed in the GDM group in our study where TC, TG, and LDL-c were increased whereas HDL-c level was decreased. Increase in triglycerides level may be due to the absorption of fat from small intestine due to HFSD intake, where fatty food leads to increase in visceral fat deposition in the early stage of pregnancy that can lead to GDM [41].

On the other hand, Vitamin D supplementation significantly lowers serum TC, TG and LDL-c levels and significantly increased HDL-c concentrations in the treated GDM group compared to untreated one.

Vitamin D was found to exert an effect on hepatic lipogenesis and gluconeogenesis. This action may be mediated via AMP-activated Protein Kinase (AMPK) activation that produces antidiabetic actions including attenuation of gluconeogenesis and lipogenesis and the promotion of glycolysis and lipid oxidation [42].

MDA level and SOD activity were also evaluated in this study to analyze the effect GDM on the antioxidant body status. MDA level was significantly increased while SOD activity was significantly decreased in GDM rats. Generally, hyperglycemia induced glucose oxidation, non-enzymatic glycation of proteins and subsequent degradation of glycated proteins are responsible for the formation of oxygen free radicals in patients with diabetes [43]. Antioxidant enzymes such as SOD and GPx are natural substances which can scavenge free radicals and prevent their deleterious effects [44].

Reactive Oxygen Species (ROS) negatively regulates the insulin pathway; leading to reduced insulin secretion and increased insulin resistance [45].Elevated ROS levels decrease the activity of the insulin signaling pathways via phosphorylation of IRS and reduction of GLUT4 gene transcription [46].

Vitamin D treatment significantly suppressed oxidative stress in our study. SOD activity in Vitamin D supplemented group increased significantly with a significant decrease in MDA level compared to GDM group. Vitamin D was documented to downregulate NADPH oxidase that produces ROS while up-regulates SOD that is responsible for converting superoxide into hydrogen peroxide [47].

In the evaluation of proinflammatory cytokines, our results show that TNF-α level was higher in the GDM group compared to control. Other studies also reported higher levels of inflammatory parameters in GDM [48,49]. The excessive production of TNF-α may be a result of oxidative stress and inflammatory changes caused by hyperglycemia [50]. TNF-α is also believed to induce insulin resistance by a number of mechanisms such as increase in serine phosphorylation of IRS-1, which disrupts the insulin signaling cascade [51].

However, Vitamin D_3 supplementation significantly decreased TNF-α level levels in the intervention group. Vitamin D is a potential negative modulator of pro-inflammatory cytokines release. It suppresses the NF-κB activation and therefore the transcription of its downstream pro-inflammatory mediators. At the same time, improved insulin signaling pathway may further inhibits the activation of NF-κB [52].

Regarding serum chemerin, its level was significantly increased in the GDM rats. This is in

agreement with the results of Ademoglu et al., [53] and Fatima et al., [48] who reported higher serum chemerin in subjects with GDM than in healthy pregnant controls. In contrast, there are reports shown that the concentration of chemerin in GDM pregnancy is lower than normal pregnancy [54]. However, Pfau et al., [55] have reported no significant difference in serum chemerin concentrations in GDM patients when compared to control group.

However, GDM rats supplemented with Vitamin D_3 showed significantly decreased serum chemerin level. In agreement with our results, Nassar and Badae [56] revealed reduced Chemerin level by Vitamin D treatment in a rat model of preeclampsia.

Moreover, serum chemerin level showed significant positive correlations with serum glucose, insulin, HOMA-IR, TC, TG, LDL-c, VLDL-c, MDA, and TNF α levels but showed significant negative correlations with serum HDL-c level and SOD activity.

Other studies also revealed significant positive correlations between serum chemerin levels and insulin resistance, and inflammatory parameters [57,58].

Results from adipose tissue explants [22] suggest that the deleterious alterations in circulating insulin levels might induce elevation of chemerin level that might be driven deleterious alterations in circulating insulin levels. This adipokine induces insulin resistance in skeletal muscle cells at the level of IRS-1 and glycogen synthase kinase 3 phosphorylation in vitro [59]. In vivo experiments also demonstrate that administration of chemerin impairs glucose tolerance, lowers serum insulin levels, and decreases basal glucose uptake in diabetic mice [60].

As the pathophysiologic mechanism of GDM is similar to T2DM in which insulin resistance and chronic inflammation are the most important pathophysiological basis, and elevated chemerin expression has been shown to contribute to the development of insulin resistance and low-grade chronic inflammation [4], it is possible that chemerin is involved in the pathophysiologic mechanisms of GDM by increasing insulin resistance and promoting subclinical inflammation [8].

Taking the present findings together, it can be concluded that Vitamin D supplementation improved the metabolic derangements (hyperglycemia & hyperlipidemia) which may be because of its genomic effects in addition to its antioxidant and anti-inflammatory capacity. Moreover, it decreased serum chemerin level that may have a role in the above mentioned improvements.

Further studies are required to investigate the potential use of combined Vitamin D_3 and chemerin receptor antagonist therapies as protective targets for GDM.

Conflict of interest: None declared.

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فيتامين د التكميلى يخفض مستوى الكميرين فى مصل دم نموذج الجرذان المصابة بداء سكر الحمل

خلفية البحث: داء الحمل السكرى هو إضطراب التمثيل الغذائى الأكثر شيوعاً والذى يؤدى إلى زيادة الإصابة بالأمراض قبل الولادة. البيانات المتعلقة بالعلاقة بين مستوى كيميرين وسكر الحمل لا تزال مثيرة للجدل. ومن ناحية أخرى فإن نقص فيتامين (د) شائع فى الحمل وقد يزيد من نسبة الإصابة بسكر الحمل.

الهدف من البحث: أجريت هذه الدراسة لدراسة آثار مكملات فيتامين (د) على مستوى كيميرين فى المصل وبعض معاملات الأيض فى نموذج سكر الحمل فى الجرذان.

مواد وطرق البحث: تم تقسيم إناث الجرذان البيضاء التى تزن ١١٣–١٣٧جم بشكل عشوائى إلى ثلاث مجموعات: المجموعة الأولى وهى مجموعة الحمل الطبيعى تتغذى على نظام غذائى عادى لمدة خمسة أسابيع قبل إحداث الحمل وتم حقنهم بالحقن البريتونى بمادة السترات فى اليوم السابع من الحمل. والمجموعة الثانية وهى المجموعة سكر الحمل المحدث تجريبياً تتغذى على نظام غذائى دهنى مضاف إليه سكر السكروز لمدة خمسة أسابيع قبل إحداث الحمل وتم بعد ذلك حقنها بالحقن البريتونى بالستربتوزوتوسين (٢٥مج/كجم من وزن الجسم) فى اليوم السابع من الحمل والمجموعة الثالثة وهى مجموعة سكر الحمل ومعالجة بفيتامين (د) تم إحداث سكر الحمل كما فى المجموعة السابقة وحقنت فى العضل ب ٢٠٠٠٠ وحدة دولية/كيلوغرام من فيتامين (د) فى اليوم الأول والرابع عشر من الحمل. وفى اليوم التاسع عشر من الحمل تم قياس كلا من مستويات الكيميرين والأستراديول والبروجسترون والجلوكوز والأنسولين ومقاومة الأنسولين والكولسترول الكلى والدهون الثلاثية والبروتين الدهنى منخفض الكثافة ومنخفض الكثافة جداً والبروتين الدهنى عالى الكثافة وعامل نخر الورم ألفا (TNF-α) ومالون داى ألدهيد (MDA) وسوبر أوكسيد ديسميوتيز (SOD) فى المصل.

النتائج: أظهرت نتائج الجرذان المصابة بسكر الحمل زيادة ملحوظة فى مستوى الجلوكوز ومقاومة الخلايا للأنسولين والكولستيرول والدهون الثلاثية والبروتين الدهنى منخفض الكثافة ومنخفض الكثافة جداً وعامل نخر الورم ألفا وأيضاً إرتفاع مستوى مالون داى ألدهيد كما وجد إنخفاض ذو دلالة إحصائية فى مستوى البروتين الدهنى عالى الكثافة والأنسولين وسوبر أوكسيد ديسميوتيز. كما كشفت النتائج أيضاً عن زيادة ملحوظة فى مستوى الكيميرين فى مصل الجرذان المصابة بسكر الحمل والذى أظهر إرتباطاً إيجابياً مع مستوى الجلوكوز والأنسولين ومقاومة الأنسولين والكولسترول الكلى والدهون الثلاثية والبروتين الدهنى منخفض الكثافة ومنخفض الكثافة جداً وعامل نخر الورم ألفا ومالون داى ألدهيد لكنه أظهر إرتباطاً سلبياً مع البروتين الدهنى عالى الكثافة وسوبر أوكسيد ديسميوتيز. ومن الجدير بالذكر أن الإمداد بفيتامين (د) قد أدى إلى تحسن ملحوظ فى هذه المعاملات فى مجموعة سكر الحمل المعالجة بفيتامين (د).

الإستنتاج: تشير نتائج هذه الدراسة إلى التأثير الوقائى لمكملات فيتامين (د) على سكر الحمل والتى قد تكون من خلال تحسين الحالة المضادة للأكسدة والإلتهابات. وقد يلعب إنخفاض مستوى الكيميرين دوراً فى هذا التأثير الوقائى.