European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 07, 2022

Original Research Article

Metabolic Role Of Leptin In Gestational Diabetes Mellitus

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Abstract

Adipose tissue acts as an endocrine gland, produce various adipokines which help in establishing communication between adipose tissue and other organs. Leptin is an important adipokine, mediating a wide range of functions like lipid and carbohydrate metabolism, insulin sensitivity, atherosclerosis, angiogenesis etc. Gestational diabetes mellitus (GDM) is a complication of pregnancy which is characterized by impaired carbohydrate tolerance with onset or first recognition during pregnancy. It develops as a result of decreased insulin sensitivity and results in altered metabolic effects like increased postprandial FFAs, increased hepatic glucose production high blood glucose levels.Leptin levels are reported to be altered, may be increased or decreased in GDM . However, report available are conflicting and fact is yet to be established. Insulin resistance in GDM has been associated with elevated leptin levels. As leptin is closely associated with lipid metabolism, it may be attributed dyslipidemias in GDM. As leptin has a wide range of metabolic roles, it may have an impact on pregnancy outcomes, both maternal as well as fetal, it is an important topic to review.

Overview

Leptin is an adipokine, secreted from adipocytes, which influences various metabolic functions. It is involved in regulation of energy intake and expenditure, influences carbohydrate metabolism by enhancing insulin secretion and sensitivity, glucose utilization, glycogen synthesis. Leptin also has an important role lipid metabolism and associated with obesity.

Gestational diabetes mellitus is defined as glucose intolerance of varying severity with onset or first recognition during pregnancy [1]. Prevalence of GDM is 7% of all pregnancies in the world. A study by Choudhary *et al* reported a prevalence of 9% of GDM in India [2].

Leptin Gene polymorphisms in Gestational diabetes

Zhang *et al*, in their meta-analysis, have narrated the role of polymorphisms of genes in GDM[3].However, there are only few studies on polymorphism of leptin gene in GDM to the best of our knowledge. Study by Hoffstedt *et al* reported an association between LEP G2548A polymorphism and elevated leptin levels [4]. The relationship between polymorphisms of leptin as well as its receptor with type 2 diabetes mellitus is well established [5,6]. Yang *et al* studied both leptin gene and its receptor polymorphism in Chinese population [7], however they didn't find any significant association between leptin gene polymorphism and GDM. Genetic polymorphisms may vary from population to population. There are no such reports available in Indian population.

Previous studies have reported *LEP* G2548A polymorphism had a strong influence on leptin gene expression [8-10], inconsistent with the results in Egyptian study by Abdel [11] and Romanian study

by Constantin *et al* [6]. An association between *LEPR* Gln223Arg gene polymorphism and leptin levels was found in Thai population studied by Suriyaprom *et al* [10], Dutch population by Rossum *et al* [12] and Romanian subjects by Constantin *et al* [6]. However, no such association was found in Turkish subjects studied by Ornek *et al* [13] and in Chinese population investigated by Yang *et al* [7], Heo[14]. But other studies suggested that *LEPR* Gln223Arg polymorphism was associated with higher insulin resistance and BMI [15].

Study by Vasku *et al* opined that subjects with AA and AG genotypes, due to their higher transcriptional activity of the LEP gene, have a significantly higher risk for gestational diabetes mellitus against those carrying the GG genotype [16]. This finding supports the hypothesis of leptin involvement in etiopathogenesis of GDM. Study by Pawlik *et al* suggested that women with the LEP rs2167270, A allele had an increased daily insulin requirement suggesting a severe form of GDM [17]. Research by Sahin *et al*. and Mammès *et al*. suggested that the LEP rs2167270 A allele is associated with increased serum leptin levels [18,19]. Hoffstedt *et al*. have shown that the rs2167270 leptin gene polymorphism influences leptin expression at the transcriptional level and hence affects the secretion of this hormone [8].

The *leptin* (*LEP*) G2548A polymorphism was found to be associated with increased leptin production and plasma secretion from adipocytes. Mutation in *leptin receptor* (*LEPR*) Gln223Arg results in impaired signaling capacity of leptin receptor [8]. Plasma leptin levels and placental leptin expression in women with GDM were significantly increased in comparison with healthy pregnant women [20,21]. Hence polymorphisms of leptin and its receptor gene could result in altered expression of their proteins.

Serum Leptin levels in Gestational diabetes

Plasma leptin levels are reported to be higher in pregnancy, peak being at 28 weeks of gestation compared to non-pregnant status . However, reports on leptin levels in GDM has been conflicting so far, as some reports suggest an elevated leptin levels [22,23], decreased [24] whereas some suggest an unaltered leptin levels in GDM [25].So it is interesting study leptin levels of GDM patients in Indian population.

In pregnancy, due to the increased fat mass and the presence of placenta, maternal leptin concentrations increase 2 to 3-fold above non-pregnant concentration, with the peak occurring around 28 weeks of gestation . As leptin may have a major role in maternal metabolism and maternal glucose homeostasis regulation, plasma leptin levels may be an important marker for predicting GDM. However, reports available on the levels of maternal leptin in GDM, are conflicting. Studies have reported an elevated leptin levels in GDM [22,23,26], diminished leptin levels [24] or insignificant differences in leptin levels among GDM patients compared to controls [25]. A study by Noureldeen *et al.* reported no significant change in leptin levels at 2nd trimester but diminished leptin levels at the 3rd trimester among GDM patients [27]. Qiu and colleagues, in their cohort study showed that for each 10 ng/ml increase in the leptin levels in early pregnancy was associated with a 20% increase in GDM risk [28]. Kautzky-Willer *et al*, in a case control study, found that plasma leptin concentrations were higher in GDM women compared with the control group in the third-trimester [22]. Such a relation was also found in the Vitoratus *et al* [29] and Qiu *et al* [23] studies. Liu *et al* [30] showed that serum leptin level is correlated with glucose tolerance during pregnancy. However, Festa *et al* [24], in a case-control study, noted that maternal third-trimester leptin concentrations were significantly lower in GDM cases as compared with controls after adjusting for possible confounding factors, such as BMI and insulin concentrations. Several possible explanations are suggested for the disparities in the existing studies.

ISSN 2515-8260 Volume 09, Issue 07, 2022

Pregnancy is considered to be leptin resistant state, which is associated with impaired leptin signaling. One possible function of increased maternal leptin levels is to enhance the mobilization of maternal fat stores to increase availability and to support trans-placental transfer of lipid substrates . There is a strong evidence that suggest placenta is the main contributor of plasma leptin rather than the adipose tissue . The fetus may be contributing to the maternal leptin load from early second trimester.

Gestational diabetes, Insulin resistance and Leptin

Insulin resistance is the key factor in the development of GDM. Reduced maternal pregravid insulin sensitivity coupled with inadequate insulin response are the causative factors for GDM.

Clinical study reports suggest that elevation of leptin levels are due to upregulation of leptin gene due to insulin resistance and hyperinsulinemia [31,32]. It has been reported that leptin affects whole body insulin sensitivity by regulating insulin mediated glucose metabolism by skeletal muscle as well as hepatic regulation of gluconeogenesis. Leptin has been found to have inhibitory effect on insulin secretion. Hence it is justifiable to study the association of Leptin gene polymorphism, circulating Leptin levels and insulin resistance in GDM.

Previous studies have suggested that leptin has an inhibitory effect on insulin gene expression and insulin secretion in pancreatic β-cells. Leptin also suppresses insulin secretion induced by cAMP, glucagon-like peptide 1 and protein kinase C . Moreover, leptin inhibits the phosphorylation of glucose transporter 2 (GLUT2) and impairs glucose transport in tissues increasing insulin resistance

It has been suggested that as gestation progresses, insulin secretion increases, reaching a maximum in the third trimester [33], whereas insulin sensitivity decreases progressively by about 70% [34]. In normal pregnancy, pancreatic beta cells compensate for the increased insulin resistance to control blood glucose [35]. However, in a pregnancy complicated by GDM, reduced insulin secretion capacity and the physiological insulin resistance that occurs on a background of chronic insulin resistance, lead to a deterioration of glucose tolerance. Studies have shown that impaired beta cell function in women with GDM is mainly attributed to decreased early-phase insulin secretion . Moreover, when insulin secretion was adjusted for the degree of insulin resistance, women with GDM had severe reduction in beta-cell function compared to normal pregnant women [36]. Ryan *et al.* demonstrated increased insulin resistance in women with GDM [37]. They reported a decrease in glucose infusion rate during euglycaemic clamp in women with GDM by 40-60% compared to pregnant non-diabetic controls and by 60-70% compared to nonpregnant controls [37]. Furthermore, increased endogenous glucose production has been reported in women with GDM compared to healthy pregnant controls [33,36]. Leptin directly affects pancreatic β-cell gene expression and leads to decrease insulin secretion [38]. Furthermore, leptin affects the β-cell proliferation, apoptosis, and cell growth. Leptin suppresses the expression of preproinsulin mRNA in pancreatic β-cells. Several signaling pathways are involved in this inhibitory role of leptin in insulin secretion.

Compared with the NGT group, higher leptin levels were found in the IFG group, consistent with the previous study [28]. Similarly, significantly higher fasting insulin levels, HOMA-IR and lower QUICKI were also noted in IFG and IGT group, namely impaired fasting glucose individuals, than NGT group. A positive and negative correlations were found between plasma leptin levels and HOMA-IR and QUICKI respectively. These correlations were confirmed in some studies [39,40], but contradicted in a few studies [41].

ISSN 2515-8260 Volume 09, Issue 07, 2022

Influence of Leptin and Lipid parameters in Gestational diabetes

GDM is known to pose a significant risk in the development cardiovascular disease(CVD) in later life. The exact mechanism is yet to be established. Altered leptin levels in GDM may play a key role in promoting CVD. Reports by Jaramillo *et al* explained the influence of leptin on body weight and percentage body fat, thereby its role in regulating adiposity signals to the brain [42]. High leptin levels have been associated with high BMI and insulin resistance in type 2 DM [43]. Bodary *et al* demonstrated atherogenic role of leptin in apoE deficient mice [44]. Study by Lekva *et al* [45] reported an elevated leptin levels associated with high TG/HDL-C ratio. Altered leptin levels along with insulin resistance in GDM patients may alter their lipid levels.

Dyslipidemia in pregnancy is well documented. After an initial decrease in the first trimester, there is a steady increase in triacylglycerols, fatty acids, cholesterol, lipoproteins, and phospholipids. The higher concentration of estrogen and insulin resistance are thought to be responsible for the hypertriglyceridemia of pregnancy.

In a study by Nawal *et al*, total cholesterol, HDL cholesterol, and apolipoprotein concentrations were not significantly different between GDM patients and control subjects[46].The results showed that there was positive correlation between leptin with cholesterol, triglyceride, and VLDL in over weight group and in obese group. The negative correlation was found between leptin with HDL in obese group [46].

Leptin synthesis is induced by hyperglycemia, hyperlipidemia, and a replete fat mass and also leptin suppresses insulin production . Leptin is expressed predominantly by adipocyte, which fits the idea that body weight is sensed as a total mass of fat in the body . Serum leptin concentration is increased in obese subjects and is closely related to fat mass and BMI and declines with weight loss . Leptin plays a central role in the long-term maintenance of weight homeostasis by acting on the hypothalamus to decrease food intake and increase energy expenditure . Serum leptin was positively & strongly correlated with BMI which is an important index of obesity. Similar correlation was reported by previous studies [47]. Positive correlation was noted between leptin & TG, negative correlation between HDL and leptin .

CONCLUSION

It could be concluded that, there may be a significant association between the gene polymorphisms of leptin and its receptor, altering leptin levels which in turn can alter insulin secretion and insulin resistance, contributing for dyslipidemias of pregnancy as well as gestational diabetes.

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