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Role of adiponectin and insulin resistance in android and gynoid obese infertile women

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ABSTRACT

Introduction: Adiponectin, a beneficial adipokine has insulin sensitizing effect and plays a prime role in human reproductive process. Obesity is associated with hormonal derangements and is found to affect the hypothalamic-pituitary-ovarian axis that results in ovulatory dysfunction and poor reproductive outcome.

Objective: The aim of our study was to investigate the role of Adiponectin and Insulin resistance in android and gynoid overweight infertile women.

Materials & methods: The cross-sectional observational study was conducted in women with BMI ≥23 in the reproductive age group of 20–40 yrs attending the infertility clinic and classified as: Group A control (n = 120) women with one or more children through natural conception and Group B with 120 infertile women (n = 120). Based on waist circumference and waist hip ratio the infertile women were sub classified as 60 android and 60 gynoid obese individuals.

After overnight fasting, blood samples were collected and analyzed for plasma glucose, serum insulin and adiponectin levels. Adiponectin was estimated by ELISA using Bio vendor Human adiponectin kit. HOMA-IR, HOMA-adiponectin and Glucose-to-insulin ratio was calculated to assess the insulin resistant state.

Result: Adiponectin levels were significantly decreased in infertile women. Based on the routine markers of insulin resistance such as fasting insulin levels, glucose to insulin ratio and HOMA-IR; 46.7%, 43%, 55% of infertile females were found to be insulin resistant respectively. Android infertile women were found to be insulin resistant as compared to the gynoid participants. Calculation of HOMA-adiponectin, an adipokine based IR marker was found to assess the severity of insulin resistance between android (0.24) and gynoid infertile (0.98) obese women. With Linear regression analysis, adiponectin presented strong significant correlation with waist circumference, LH, HOMA-IR and HOMA-adiponectin as compared to the gynoid infertile women.

Conclusion: Adiponectin, the beneficial adipokine levels are found to be decreased in obese infertile females due to visceral adiposity that results in insulin resistance. HOMA-adiponectin is an adipokine based insulin resistance marker that discriminates android from gynoid infertile females. Life style modifications benefit the overweight infertile women that modulate in reducing the visceral fat mass and thereby increase adiponectin levels.

1. Introduction

Adiponectin is a beneficial adipokine that links obesity and the reproductive process. It is an insulin-sensitizing hormone and their levels are associated with the normal ovulatory process and contribute to better effects in assisted reproductive cycles (ZhangPronyuk et al., 2015). Human adipocytes contribute to the production of compounds that has important effects on reproductive function and fertility.

Adiponectin, a 30 kDa molecule is produced abundantly by the adipose tissue. Adiponectin, an insulin sensitizer is actively involved in the metabolic process in the insulin-sensitive tissues. The role of insulin-sensitizing function of adiponectin is supported by the evidence (i) inverse relationship between insulin resistance and adiponectin (ii) chromosome 3 (3q27) gene linked to Diabetes mellitus includes the adiponectin gene (iii) adiponectin has anti-atherogenic properties and insulin-sensitizing effects (Ardawi and Rouzi, 2005).

Lowered adiponectin gene expression in visceral adipose tissue is an important determinant that reflects insulin resistance (Michalakis and Segars, 2010). Adiponectin is involved in regulating the hypothalamic-pituitary-ovarian axis thereby decreased levels of adiponectin contributes to chronically elevated LH that causes ovulatory dysfunction and results in infertility (Lu et al., 2008). The complex interaction

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between adiponectin and insulin at a molecular level facilitates insulin-sensitizing effects by binding to its receptors on target tissues (Ardawi and Rouzi, 2005).

Insulin resistant state is a physiological condition in which insulin receptors are not responding to the hormone insulin. Excess visceral adiposity results in insulin-resistant state and thereby compensatory hyperinsulinemia is triggered. As a consequence of hypertrophic adipocyte, there occurs decreased adiponectin and an altered production of free fatty acids, TNF-alpha, leptin, resistin that suppresses insulin sensitivity. Insulin resistance and hyperinsulinemia inhibits the normal ovulatory process, failure of implantation and pregnancy loss (Sakumoto et al., 2010).

In the android obesity profile, there is excess visceral adiposity accumulation around the abdomen. Measurement of waist circumference gives the approximate measure of upper body obesity (BMI ≥ 23, waist-hip ratio ≥ 0.85 and WC ≥ 88 cm). In the gynoid obesity profile, excess subcutaneous adiposity accumulation is seen around the hip that contributes to lower body obesity (BMI ≥ 23, waist-hip ratio < 0.85 and WC < 88 cm) (Wiklund et al., 2008; Kirchengast and Huber, 2004). Literature inconsistency still exists to evaluate the role of adiponectin levels in android and gynoid obese infertile women. The study aims to assess the role of serum adiponectin levels in android and gynoid obese infertile women.

2. Materials and methods

This observational cross-sectional study was conducted in infertile females in the reproductive age group of 20–40 yrs attending the infertility clinic, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India. Before the commencement of the study, research protocols were reviewed and approved by the SRM Institutional Ethics Committee (IEC: No: 963/IEC/2016). The study purpose was explained to the participants and written informed consent was obtained from all the participants.

2.1. Inclusion criteria

The females in the age group of 20–40 years who attended the infertility OP clinic were enrolled for the study. About 120 participants were enrolled in the study protocol with the following inclusion criteria: (i) Primary infertility (ii) BMI ≥ 23 (overweight and obese) (iii) irregular menstrual cycle or ovulatory dysfunction (ultrasound finding) or presence of polycystic ovaries (according to Rotterdam's criteria). Infertile participants were further categorized as Android obese n = 60 with a waist circumference more than 88 cm and WHR ≥0.85 and Gynoid obese n = 60 based on waist circumference less than 88 cm and WHR < 0.85.

2.2. Exclusion criteria

Infertile participants with uterine anatomical defect, thyroid dysfunction, diabetes mellitus, and pregnant women were excluded from the study.

Healthy females of the same age group with at least one live birth through natural conception, regular menstrual cycle, without any major systemic illness or related problems referred through the routine master health check-up were enrolled as controls.

Initial evaluation included detailed medical and menstrual history based on the pre-designed questionnaire format and preliminary clinical examination was carried out by the Gynecologists. Transvaginal Ultrasonography scanning was done to check for uterine, tubal abnormality and presence of polycystic ovaries.

2.3. Anthropometric measurements

Weight (Kg), height (meters), waist circumference (cm) and hip circumference (cm) were measured. The anthropometrics indices BMI and waist-hip circumference ratio were calculated. The Standard Consensus statement for the Indian population was considered as the cut-off for BMI (Misra et al., 2009, Vilela et al., 2016).

3. Sample collection and analysis

In the second or third day of the menstrual cycle after overnight fasting of 10–12 h, venous samples were collected from the participants. Since some of the patients had irregular periods, investigations were done independently of the day of the menstrual cycle. Serum Adiponectin levels were analyzed BIO-RAD ELISA instrument using the Human Adiponectin Bio vendor 96 wells ELISA kit (normal reference range: 4–12 μg/mL).Serum TSH, FSH, LH, prolactin and insulin were assayed on the day of sample collection in automated Hormone analyzers based on the method Chemiluminescence with standard reagent kits. Fasting plasma glucose was estimated in Autoanalyzer Beckman Coulter AU 480 (Hexokinase method). The remaining samples were stored in −20 °C deep freezer until further analysis. The markers of insulin resistance such as elevated fasting insulin levels (> 15μIU/mL) and HOMA-IR was calculated with (Fasting insulin X FPG)/405 [14]. Glucose to insulin ratio was calculated as Fasting plasma glucose/ Fasting Insulin. The G/I value of > 4.5 is considered as insulin sensitive and G/I value of ≤4.5 as Insulin resistant individuals. HOMA-Adiponectin was calculated using the formula (Fasting insulin X FPG)/ (405 X adiponectin μg/ml) (Vilela et al., 2016).

4. Statistical analysis

Statistical analysis was performed with SPSS version 21.0. With Linear regression analysis, statistical significance was compared for the biochemical parameters between the groups. For all the statistical analysis, p-value < 0.05 was considered statistically significant.

5. Results

In this study, 354 infertile women were screened, out of which 120 primary infertile female participants of the same age group and Body mass index ≥23 were recruited as they satisfied the inclusion criteria. Table (1) presents the basic anthropometric and biochemical parameters in the study.

The mean Adiponectin levels were decreased in infertile females (7.35 ± 3.19) (μg/ml) as compared to the healthy participants (13.025 ± 2.62) μg/ml and showed the significant statistical difference with 'p' value < 0.0001. The mean fasting insulin levels were high in infertile women as compared to the controls with a significant statistical difference.

Insulin resistance was assessed based on fasting insulin levels ≥15 μIU/ml, it was found that 46.7% were found to be insulin resistant. Based on Glucose to insulin ratio, 43% were found to be insulin resistant. Using the HOMA-IR calculation, we found 55% of the infertile females to be insulin resistant.

In Table 2, android obese infertile females with WC ≥ 88 cm and WHR (≥0.85) and (Table 3) gynoid obese infertile females with waist circumference < 88 cm and WHR (< 0.85) were analyzed to assess Insulin resistance with variables such as fasting insulin, Glucose to insulin ratio, HOMA-IR, and HOMA-adiponectin in both android and gynoid group (see Table 4).

As per Table (5): Insulin resistance was assessed in infertile females with gynoid obese and android obese infertile females based on fasting insulin, Glucose to insulin ratio, HOMA-IR and HOMA-adiponectin, with statistically significant p value < 0.05.

In Table (6), The impact of adiponectin on biochemical parameters such as hormonal profile and markers of insulin resistance and with anthropometric variables in android and gynoid infertile women was studied using Linear regression analysis. Fig. 1, represents the

Table 1
Comparison of Anthropometric and Biochemical characteristics between the controls and infertile women.

Parameters	Group A CONTROL (n = 120)	Group B INFERTILE (n = 120)	P value
ANTHROPOMETRIC VARIABLES			
AGE (yrs)	28.4 ± 5.2	28.7 ± 4.95	NS
WT (kg)	56.96 ± 6.31	63.03 ± 5.41	< 0.001**
HT (mt)	1.54 ± 0.032	1.55 ± 0.037	NS
BMI (kg/mt^2)	24.94 ± 2.27	28.44 ± 2.18	< 0.05*
WC (cm)	84.44 ± 5.83	89.67 ± 6.55	< 0.002**
HC (cm)	101.31 ± 7.19	103.35 ± 4.34	NS
WHR	0.834 ± 0.033	0.865 ± 0.031	< 0.05*
WC/Height ratio	0.48 ± 0.21	0.61 ± 0.09	< 0.005
BIOCHEMICAL VARIABLES			
ADIPONECTIN(μg/ml)	13.025 ± 2.62	7.35 ± 3.19	< 0.0001***
INSULIN (μIU/ml)	7.68 ± 3.21	13.87 ± 6.378	< 0.001**
HOMA –IR	2.05 ± 0.87	4.19 ± 1.67	< 0.05*
G/I ratio (mg/10^{-4} U)	15.32 ± 4.91	7.9 ± 5.37	< 0.001**
FPG (mg/dL)	92.73 ± 6.73	101.7 ± 11.47	< 0.002**

Values are expressed in Mean ± Standard Deviation.
*P value < 0.05 is considered significant.
NS- Not significant.
***Very Highly significant **Highly Significant.

Table 2
Comparison of biochemical variables and Adiponectin between Android obese females (controls) and infertile Android obese females (study).

Parameters	Android Obese control (n = 60)	Android Obese Infertile (n = 60)	P value
Adiponectin (μg/ml)	11.57 ± 2.048	5.94 ± 2.03	< 0.0001***
Insulin μIU/ml	9.49 ± 2.1	16.87 ± 5.57	< 0.0001***
Glucose/Insulin ratio (mg/10^{-4} U)	11.46 ± 3.43	6.89 ± 3.64	< 0.0001***
HOMA-IR	2.046 ± 0.56	4.16 ± 1.48	< 0.0001***
HOMA-Adiponectin	0.267 ± 0.09	0.98 ± 0.78	< 0.0001***

Values are expressed in Mean ± Standard Deviation.
P value < 0.05 is considered significant.
NS- Not significant.
***Very highly significant **Highly Significant.

comparison of adiponectin levels between andriod and gynoid infertile and respective controls.

6. Discussion

Adiponectin the key adipokine signifies the essential hormonal link between visceral adiposity and the reproductive process.

The study highlights the presence of hypoadiponectinemia in obese infertile females. This finding is consistent with many studies that have observed that adiponectin is the only beneficial adipokine which is

Table 4
Comparison of Hormonal pattern between the android and gynoid infertile women.

Parameters	Android obese (n = 60)	Gynoid obese (n = 60)	P value
FT3	2.64 ± 0.41	3.2 ± 0.5	NS
FT4	0.94 ± 0.21	1.072 ± 0.2	NS
TSH	3.17 ± 1.48	2.83 ± 1.25	NS
LH	10.42 ± 5.507	6.73 ± 3.74	< 0.0001***
FSH	4.58 ± 1.665	4.197 ± 2.71	< 0.24 NS
LH/FSH	2.04 ± 0.985	1.19 ± 0.63	< 0.0001***
Estradiol	38.66 ± 14.765	49.84 ± 22.1	< 0.0001***
Prolactin	16.74 ± 9.47	28.32 ± 13.78	< 0.0001***

Values are expressed in Mean ± Standard Deviation.
P value < 0.05 is considered significant.
***Very Highly significant **Highly Significant *significant.

Table 5
Comparison of biochemical parameters to assess insulin resistance in android and gynoid infertile women.

Parameters	Gynoid obese (n = 60)	Android obese (n = 60)	P value
WC (cm)	85.12 ± 2.81	92.9 ± 3.81	< 0.0001***
Adiponectin (μg/ml)	8.49 ± 2.58	5.94 ± 2.03	< 0.0001***
INSULIN (μIU/ml)	9.34 ± 3.72	16.87 ± 5.57	< 0.0001***
G/I Ratio (mg/10^{-4} U)	12.25 ± 6.023	6.89 ± 3.64	< 0.0001***
FPG (mg/dL)	96.604 ± 7.335	103.52 ± 12.02	< 0.0001***
HOMA –IR	2.23 ± 0.922	4.73 ± 1.32	< 0.0001***
HOMA - Adiponectin	0.237 ± 0.161	0.98 ± 0.78	< 0.0001***

Values are expressed in Mean ± Standard Deviation.
P value < 0.05 is considered significant.
***Very Highly significant **Highly Significant *significant.

decreased in obese individuals with increased visceral adiposity (Misra et al., 2009; Ramanand et al., 2014a).

6.1. Adiponectin and WC

Serum adiponectin levels were significantly decreased in infertile females than healthy controls. The results of the present study agrees with the finding that circulating adiponectin levels decrease with increased waist circumference, WHR, thus highlights the influence of visceral adiposity (Achari and Jain, 2017; Comim et al., 2013). The molecular mechanism identified is that an adiposity cytoplasmic factor constitutively inhibits translation of the adiponectin gene in obese individuals (Banga et al., 2009).

6.2. Adiponectin and hormonal effects that affects ovulation

Adiponectin has a major role in the initiation of preovulatory changes in the ovary, modulates ovarian steroidogenesis, oocyte

Table 3
Comparison biochemical variables and Adiponectin between Gynoid obese females (controls) and infertile Gynoid obese females (study).

Variables	Gynoid Obese Controls (n = 60)	Gynoid obese Infertile females (n = 60)	P value
Adiponectin (μg/ml)	12.91 ± 2.71	8.49 ± 2.58	< 0.05*
Insulin μIU/ml	7.38 ± 2.14	9.34 ± 3.72	< 0.001**
Glucose/Insulin ratio (mg/10^{-4} U)	14.31 ± 4.6	12.25 ± 6.023	< 0.005**
HOMA-IR	1.77 ± 0.575	2.23 ± 0.922	< 0.001**
HOMA-Adiponectin	0.165 ± 0.097	0.237 ± 0.161	< 0.05*

Values are expressed in Mean ± Standard Deviation.
P value < 0.05 is considered significant.
NS- Not significant.
***Very Highly significant **Highly Significant *significant.

Table 6
Correlation of Adiponectin with anthropometric variables, Hormone pattern, Markers of Insulin resistance in android and gynoid infertile women.

Parameters	Android obese (n = 60) R value	P value	Gynoid obese (n = 60) R value	P value
ANTHROPOMETRIC VARIABLES				
WC (cm)	**0.93** [b]	< **0.0001** [c]	0.01	NS
HC (cm)	0.03	NS	**0.85** [b]	< **0.0001** [c]
WHR	0.50	< 0.001	0.66	< 0.001
HORMONES				
LH	**0.48**	< **0.001**	0.003	0.53
FSH	0.11	0.33	0.038	0.08
LH/FSH	**0.42**	< **0.01**	0.052	0.028
Estradiol	0.23	< 0.05	0.21	< 0.05
MARKERS OF INSULIN RESISTANCE				
FPG (mg/dL)	0.054	0.03	0.002	0.87
INSULIN (μIU/ml)	**0.864** [b]	< **0.0001** [c]	0.59	< 0.01
G/I Ratio ($mg/10^{-4}$ U)	0.621 [b]	< 0.001	0.53	< 0.01
HOMA –IR	**0.864** [b]	< **0.0001** [c]	0.68	< 0.001
HOMA - ADN	**0.75** [b]	< **0.0001** [c]	0.574	< 0.001

a **Correlation** Small (0.3–0.1) Medium (0.5–0.3) Strong (1.0–0.5).
b **Shows strongest correlation**.
c **Indicates highly significant**.

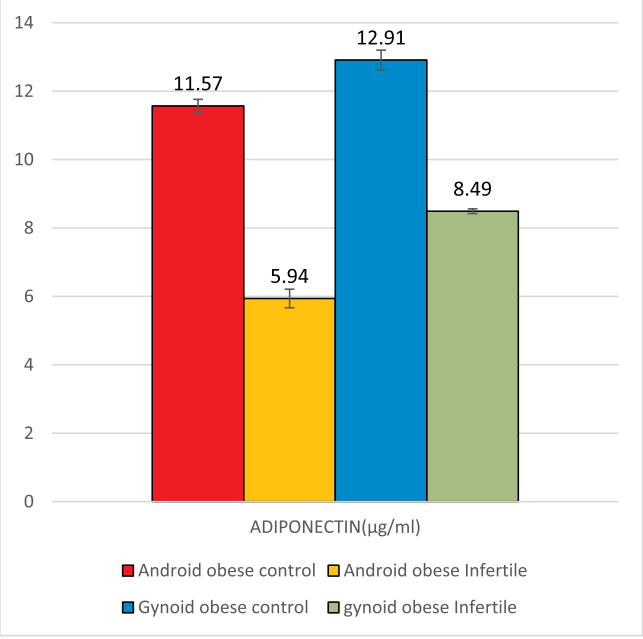

Fig. 1. Represents the Adiponectin levels between Android and Gynoid obese infertile women.

maturation and ovulation (Dağ1 and Dilbaz, 2015). In the present study, there was significant correlation between adiponectin, LH levels and LH/FSH ratio in android obese women.

Evidence has proved the beneficial role of adiponectin on folliculogenesis where adiponectin deficiency disrupts FSH and LH surge which explains the disturbed ovulatory function (Cheng et al., 2016). A decreased level of Adiponectin contributes to lowered expression of cytochrome p450 family enzyme (CYP11A1) which is involved in progesterone synthesis. Thus novel mechanism links adiponectin with female infertility which regulates reproductive hormonal balance and ovarian follicle development (Cheng et al., 2016; Seth et al., 2013).

6.3. Adiponectin and insulin resistance

The mean serum insulin levels were elevated in infertile individuals suggesting insulin resistance is more common in android infertile women. Furthermore, insulin resistance assessed by HOMA-IR revealed 55% of individuals were insulin resistant than assessed by Glucose to insulin ratio that presented with 43% individuals with insulin resistance. Moreover HOMA-IR is an index of peripheral insulin sensitivity. Hyperinsulinemia is triggered by the accumulated visceral fat which is less sensitive to insulin due to increased lipolysis with increased FFA and pro-inflammatory cytokines subsequently leading to insulin resistant state. IR affects granulosa cells and arrests the follicle growth resulting in ovulatory disturbances (Yadav et al., 2011).

6.4. Impact of adiponectin in android and gynoid obesity

Analysis of anthropometric and biochemical findings between android obese infertile and their controls revealed that Android obese females presented with elevated WC, fasting insulin level, HOMA-IR, HOMA-Adiponectin; and decreased serum adiponectin levels and glucose to insulin ratio compared to android obese infertile females with a very high statistical difference. This directly reflects that in android obese individuals excess visceral fat is more associated with insulin resistance and severity resulted in disturbed ovulatory process (Yadav et al., 2011; Sirbu et al., 2018a). This is supported by the researcher that Adiponectin concentration predicts increased visceral adiposity and an important determinant of insulin resistance especially in android obese individuals (Lopes et al., 2016; Pangaribuan et al., 2011; Ramanand et al., 2014b).

Whereas in gynoid obese infertile the adiponectin levels were decreased as compared with the controls and adiponectin showed statistically significant correlation with hip circumference. One of the research works have concluded that adiponectin deficiency leads to female subfertility which is supported by the molecular events that are independent of insulin sensitivity. Novel mechanism linking adiponectin and ovulation is that i) altered peak concentration of LH surge ii) lowered expression of cytochrome p450 which is critical for progesterone synthesis I ii) increased pro-apoptotic factors (Sirbu et al., 2018b).

6.5. Beneficial adiponectin and its molecular mechanism

The beneficial adiponectin has direct peripheral effects on the reproductive tissues that regulate ovulatory follicle development which enhances ovum maturation and ovulation, successful implantation and pregnancy (Kawwass et al., 2015). Adiponectin exerts its insulin-sensitizing effects by direct cross-talk with insulin signaling cascades (Balsan et al., 2015). Moreover, at the molecular level, adiponectin converges with insulin signaling pathways through the adapter protein APPL1 that potentiates insulin action at peripheral reproductive tissues. The decreased adiponectin levels in obese infertile females are consistent with the fact that reduced APPL1 expression contributes to IR (Cheng et al., 2014).

6.6. Adiponectin and HOMA-adiponectin

In the present study, HOMA-adiponectin, an adipokine based insulin resistance marker was utilized to differentiate and assess the insulin sensitivity between android and gynoid obese individuals.

In android individuals, HOMA-adiponectin is elevated that reflects insulin resistance and adiposopathy in android individuals than the gynoid obese individuals. Thus in the present study, the findings of decreased Adiponectin were consistent with substantially increased WC, HOMA-IR, HOMA-adiponectin in android obese infertile women. This is further supported by the fact that HOMA-adiponectin that closely mirrors HOMA-IR can be used for screening of insulin resistance in

infertile women (Seth et al., 2013) that can decide the initial treatment modality of weight reduction in android females.

The present study concludes that obese individuals have increased visceral adipose tissue that suppresses the beneficial adipokine Adiponectin synthesis. Reduced adiponectin reduces insulin sensitivity in reproductive tissues, entails regulation of reproductive hormonal balance thereby resulting in disturbance in the ovulatory process and causes infertility.

7. Conclusion

The beneficial Adiponectin levels are decreased in obese infertile females due to visceral adiposity resulting in insulin resistance. HOMA-adiponectin is an adipokine based insulin resistance marker of central obesity that can differentiate the severity of insulin resistance between android and gynoid obese individuals. Lifestyle modifications and weight reduction can improve adiponectin levels and thereby insulin-sensitive environment is favored resulting in the regular menstrual cycle, ovulatory process, and successful fertility.Acknowledgement

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Conflicts of interest

None.

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