Assessment of Homocysteine Plasma Levels and Insulin Resistance among Obese Women with Anovulatory Infertility

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Abstract: This study was conducted to assess homocysteine plasma level and insulin resistance profile (blood glucose level, plasma insulin level, HOMA-IR, body mass index) among different groups (non-obese, over-weight and obese) of women with anovulatory infertility. This cross-sectional study was conducted in Suez Canal University hospital in the period from December 2011 to August 2012. Total of 150 women with anovulatory infertility were included in this study, divided equally into three groups: non-obese, over-weight and obese. Blood samples were collected in second or third day of menstrual cycle for laboratory work-up. Hormonal profile and insulin resistance profile were determined for each patient. Plasma level of homocysteine was determined using the commercially available ELISA kit. Results showed that there were statistically significant differences between the three groups regarding homocysteine plasma level, body mass index and HOMA-IR with p-value < 0.001. There was a significant association between homocysteine plasma level and BMI. BMI and serum testosterone level were higher in obese and over-weight women in comparison to non-obese patients. Positive correlations were found between homocysteine plasma level with insulin level, HOMA-IR and LH/FSH ratio. In conclusion, homocysteine plasma level is positively correlated with BMI, insulin resistance, testosterone level and LH/ FSH ratio in over-weight and obese infertile women. This highlights an interaction between high homocysteine level, insulin resistance and hyperandrogenemia, mimicking polycystic ovarian syndrome that could be responsible for the infertile state in these patients.

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1. Introduction

Infertility occurs in 13 to 21% of married couples of reproductive age. One of the most common causes of infertility in women of reproductive age is chronic anovulation (ESHRE Capri, 2012). Polycystic ovary syndrome (PCOS) is responsible for 70% of cases of anovulatory infertility (Thanyarat *et al*, 2012).

Many authors showed that there is a strong correlation between plasma homocysteine concentrations and BMI (Elshorbagy *et al*, 2008; Zoppini *et al*, 2008; Elshorbagy *et al*, 2009) homocysteine levels may be elevated in patients with chronic anovulation and PCOS and may play a role in endothelial damage that occurs in these patients (Stefano *et al*, 2009).

Homocysteine is derived from the metabolic conversion of the essential amino acid methionine. Metabolism of homocysteine is via one or two pathways either trans-sulfuration or re-methylation. In the re-methylation pathway of homocysteine to methionine, vitamin B12 and folate act as cofactors (Fowler, 1997). One of the essential enzymes in the re-methylation process is methylene-tetra-hydro-folate reductase (MTHFR) (Goyette *et al*, 1994). Hyperhomocytenemia occurs mainly due to genetic defect in this enzyme & other deficiencies in vitamin cofactors (folate Vitamin B 12). It may also be associated with certain chronic medical conditions and drugs such as fibrates and nicotinic acid (Cabarkapa *et al*, 2007).

Major determinants of plasma homocysteine levels are folate, vitamin B12 and B6 intake, renal function, and to a lesser extent cigarette smoking, arterial hypertension, hypercholesterolemia, physical exercise, coffee consumption, and alcohol consumption (Kazemi *et al*, 2006). In addition, individuals homozygous for the thermo-labile form of MTHFR also show higher levels of homocysteine, mainly in the presence of low folate (Rozen, 1997).

Hyperhomocystenemia is an independent risk factor for atherosclerotic vascular disease, cerebro-vascular events and recurrent venous/ arterial thrombo-embolism (Dierkes *et al.*, 2004). The mechanisms by which hyperhomocystenemia may predispose to arterial thrombosis are not entirely clear but consist of endothelial cell damage (Blundell *et al.*, 1996), inhibition of fibrinolysis (Bienvenu *et al.*, 1993), activation of the coagulation cascade (Freyburger *et al.*, 1997), impaired generation of

nitric oxide and prostacyclin (Stamler *et al.*, 1993), and enhanced collagen production by smooth muscle cells (Majors *et al.*, 1997).

Hyperhomocystenemia can induce insulin resistance (Welch and Loscalzo, 1998) leading to compensatory hyper-insulinemia, which may impair the activity of MTHFR and CBS enzymes leading to accumulation of homocysteine in plasma (Dicker-Brown *et al.*, 1999). Thus insulin levels have also been observed as a modulating factor of homocysteine as it inhibits hepatic cystathione β-synthase activity (McCarty, 2000). Insulin resistance or consuming a high insulinaemic index diet will tend to increase plasma homocysteine (Meigs *et al.*, 2001).

This study was carried out to evaluate homocysteine plasma level and its correlation with insulin resistance in non-obese, over-weighted and obese women with anovulatory infertility.

2. Methods:

This cross-sectional study was conducted in Suez Canal University hospital in the period from December 2011 to August 2012. This study was approved by the Ethics Committee of the Suez Canal University and carried out in accordance with the principles of Helsinki Declaration. One hundred and fifty infertile women were included in this study divided equally into three groups: non-obese, over-weight and obese.

Exclusion criteria included women with hyperprolactinemia, chronic diseases, endocrinal diseases, women on medications such as steroids, hypertension, diabetes mellitus, cardio-vascular diseases, any other medications known to affect plasma level of homocysteine.

An informed consent was obtained from each patient. All patients underwent physical and laboratory work-up. Physical examination included measurement of body weight, height and calculation of BMI. Patients were classified according to their BMI to non-obese (<25 kg/m^2), over-weight (25-30 kg/m^2) and obese (>30 kg/m^2).

Blood samples were taken from each patient on the second day of the menstrual cycle. Fasting blood glucose was determined using fully-automated auto-analyzer Hitachi 912 (Roche Diagnostics, Germany). Levels of fasting insulin, testosterone, TSH, FSH and LH were determined using chemiluminescent enzyme immune-assay techniques on Cobas e411 (Roche Diagnostics, Germany). Homocysteine plasma level was determined using commercially available kit DRG® Homocysteine (DRG International Inc., USA).

Insulin resistance was determined after using Homeostasis Model Assessment Insulin Resistance (HOMA-IR). HOMA-IR more than 2.5 was considered insulin resistant.

Anovulation was diagnosed clinically using folliculometry and low mid-luteal serum progesterone level. Trans-vaginal ultrasound was done for every patient on days 9, 11, and 13 of the menstrual cycle. Anovulation was diagnosed when there is failure of the ovaries to produce mature follicle in two successive cycles.

Collected data was analyzed using the Statistical Package for Social Sciences version 13 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as means and standard deviations (SD). Comparison between study groups was done using analysis of variance (ANOVA). The means of continuous variables were compared by student't' test. Association between characteristics and laboratory test results were assessed by Pearson's bi-variate correlation analysis. Statistical significance was set at *p*-value less than 0.05.

3. Results:

This study included 150 infertile women divided equally into three groups with comparable age. However, there were significant differences between the three groups regarding BMI, homocysteine plasma level, insulin level and HOMA-IR with *p*-value < 0.001 (Table 1).

Hyperhomocysteinemia was found in 75% of the obese women; however it affected only 31% of the over-weight and 3.5% of the non-obese women. This suggests a significant association between high homocysteine plasma level and high BMI. HOMA-IR was higher among obese women than among over-weighted and non-obese women with *p*-value <0.001 (Table 1).

Table 1: Comparison between the three study groups:

Character	Obese	Over-weighted	Non-obese	*p*-value
Age (years)	29 ± 7	28 ± 8	26 ± 7	0.687
BMI (kg/ m^2)	32.2 ± 0.94	27.6 ± 1.38	23 ± 0.96	< 0.001
FBS (mg/ dl)	92 ± 12	89 ± 15	91 ± 13	0.819
Insulin level (µU/ ml)	27.4 ± 9.91	15.6 ± 8.5	11.4 ± 2.8	< 0.001
Homocysteine (µmol/ L)	15.78 ± 4.34	10.19 ± 5.32	8.66 ± 2.14	< 0.001
HOMA-IR	6.02 ± 1.96	3.08 ± 0.98	2.12 ± 0.89	<0.001

BMI: Body Mass Index, FBS: Fasting Blood Sugar, HOMA-IR: Homostasis Model Assessment Insulin Resistance

About 56% of over-weight and obese women had insulin resistance. When both obese and over-weight women (100 women) were categorized according to insulin resistance, homocysteine plasma level was significantly higher in those with insulin resistance than those without insulin resistance with *p*-value < 0.001. In addition, there were statistically significant differences between both groups regarding BMI, Insulin level and HOMA-IR with *p* -value < 0.001 (Table 2).

Table 2: Categorization of obese and over-weighted women according to insulin resistance:

Character	With insulin resistance	Without insulin resistance	*p* -value
Age (years)	29 ± 5	28 ± 6	0.88
BMI (kg/ m^2)	30.2 ± 1.11	26.3 ± 1.09	< 0.001
FBS (mg/ dl)	93 ± 10	87 ± 11	0.461
Insulin level (µU/ ml)	29.21 ± 5.19	8.71 ± 3.22	< 0.001
Homocysteine (µmol/ L)	15.11 ± 3.66	9.22 ± 4.08	< 0.001
HOMA-IR	6.23 ± 1.61	1.88 ± 0.44	< 0.001

BMI: Body Mass Index, FBS: Fasting Blood Sugar, HOMA-IR: Homostasis Model Assessment Insulin Resistance

Regarding the hormonal parameters, comparisons between the three groups showed no significant differences in the level of TSH, FSH or LH. However, a significant difference was detected in the testosterone level (p value < 0.001) (table 3).

Table 3: Sex hormone levels in the three study groups:

Item	Obese	Over-weighted	Non-obese	*p*-value
LH (IU/ ml)	12.44 ± 5.98	9.61 ± 3.76	7.54 ± 2.89	0.468
FSH (IU/ L)	6.81 ± 2.71	6.18 ± 3.01	4.89 ± 1.89	0.729
TSH (mIU/ L)	4.81 ± 2.38	4.21 ± 1.91	3.45 ± 2.02	0.382
Testosterone (nmol/ L)	2.26 ± 0.79	1.74 ± 0.82	1.27 ± 0.67	< 0.001

LH: Luteinizing Hormone, FSH: Follicular Stimulating Hormone, TSH: Thyroxin Stimulating Hormone

LH/FSH ratio was higher among obese and over-weight women with insulin resistance than those without insulin resistance with *p* -value 0.002 (Table 4). Although the level of total testosterone was also higher among infertile women with insulin resistance than those without insulin resistance, but there was no significant difference between the two groups with *p* -value 0.191 (Table 4).

Table 4: Hormonal profile among obese and over-weight women with and without insulin resistance:

Item	With insulin resistance	Without insulin resistance	*p*-value
LH (IU/ ml)	13.39 ± 4.21	8.21 ± 3.02	0.002
FSH (IU/ L)	6.15 ± 3.19	6.78 ± 2.83	0.816
LH/FSH ratio	2.39 ± 1.54	1.42 ± 1.08	0.002
TSH (mIU/ L)	5.03 ± 2.19	3.78 ± 1.72	0.271
Testosterone (nmol/ L)	2.03 ± 0.78	1.81 ± 0.89	0.191

LH: Luteinizing Hormone, FSH: Follicular Stimulating Hormone, TSH: Thyroxin Stimulating Hormone

Correlation analysis was done between homocysteine plasma level and different demographic and laboratory parameters. Homocysteine plasma level was positively correlated with BMI, insulin level, fasting blood glucose level, LH/FSH ratio, HOMA-IR and testosterone level. However, no correlation was found between homocysteine plasma level and patients' age, TSH level, LH level or FSH level (Table 5).

Table 5: Correlation analysis between homocysteine plasma level and different demographic and laboratory items:

Item	r	*p*
Age	- 0.256	0.411
Body mass index	0.521	< 0.001
Fasting blood glucose level	0.431	0.006
Insulin level	0.361	< 0.001
Luteinizing hormone level	0.295	0.318
Follicular stimulating hormone level	- 0.199	0.461
LH/FSH ratio	0.493	< 0.001
Thyroxin stimulating hormone level	- 0.271	0.384
Testosterone	0.417	< 0.001
Homostasis Model Assessment Insulin Resistance	0.562	< 0.001

4. Discussion:

Homocysteine is normally a sulfur amino acid that is formed by the trans-methylation of methionine amino acid. It can retransform into methionine amino acid by re-methylation, accompanied by folate and vitamin B12, as well as into cysteine amino acid by cystathionine-β-synthase enzyme mediated with vitamin B6. Cystathionine-β-synthase enzyme deficiency is associated with premature atherosclerosis and recurrent thrombo-embolic events in homocystinuria. In addition, nutritional (folic acid and vitamins B6 and B12), genetic (methylenetetrahydrofolate reductase gene mutations), and endocrine factors, as well as cancer, human immunodeficiency virus, and renal failure, have been claimed as conditions responsible for moderately high levels of homocysteine (Glowinska *et al*, 2003).

Recently, there have been several studies showing an association between plasma level of homocysteine and obesity. However, some conflicting results were also reported. In this study, results revealed changes in the homocysteine levels according to BMI and insulin resistance among the three study groups.

The study revealed higher homocysteine levels as well as more insulin resistance (represented by HOMA-IR) among obese infertile women than among over-weight and non-obese infertile women. This noticed the association of increases in the insulin resistance with higher BMI. Homocysteine plasma levels were highly correlated with BMI and insulin resistance (HOMA-IR) among obese women, with no correlation with patient age. These results are in agreement with a study done by Howard *et al.* who concluded a significant interaction between increasing obesity and insulin resistance (Howard *et al*, 2004). Conversely, Vivian Fonseca *et al.* (2003) concluded that there was no correlation between homocysteine levels and BMI.

Although patients in the three groups were of comparable age, homocysteine plasma levels were significantly different. However, Henry et al concluded that plasma homocysteine levels showed an increasing trend with age (Henry, 2011).

In our study, results revealed higher insulin levels among obese women than among both over-weight and non-obese ones. In a prospective study on middle aged women, Guthrie *et al.* (2001) found that although increases in insulin levels were independent of age, they were positively associated with increases in BMI. Siegfried *et al.* (2000) concluded in their study that insulin is a main correlate of homocysteine in obese children and adolescents and suggested that hyperinsulinism may contribute to impairment of homocysteine metabolism in childhood obesity.

The coexistence of severe insulin resistance and hyper-insulinemia has been demonstrated, whereby hyperinsulinemia is considered secondary to the defects in insulin action but has also been implicated in the development and maintenance of excess obesity. In agreement with the assumption that hyperinsulinemia contributes to elevated homocysteine levels,

Jacobs *et al.* (1998) demonstrated an increased activity of trans-sulfuration enzymes and consecutive decreased homocysteine levels in rats with streptozotocin induced diabetes. This effect was reversible after insulin treatment.

In this study, results showed higher homocysteine levels among obese and over-weight women with insulin resistance than among those without insulin resistance. This finding was comparable to results of a study done by James *et al.* (2001) who had reported a positive association between levels of plasma homocysteine and some individual traits associated with insulin resistance.

Sex steroid hormones and androgens appeared to influence the metabolism of homocysteine and have been found to increase its plasma levels. In the present study, results revealed association between homocysteine levels and testosterone level as well as LH/FSH ratio. These findings might suggest the association of Polycystic Ovarian Syndrome (PCOS) with this state of hyper-androgenemia and high homocysteine plasma level. Similar results were obtained by Sachan *et al* .(2012). In contrast to this finding, George E et al found that DHEAS and testosterone level were not related to homocysteine level (George *et al.*, 2006). However, Randolph *et al.* (2006) found, in his cross-sectional study, variations in all body hormonal assays, positively with testosterone level and negatively to all the others. A genetic study done by Maristella *et al.* highlighted that homocysteine metabolism may be involved in patho-physiology of these cases of un-explained female sterility (UFS) because of the association between hyperhomocysteinemia, low serum folate and TT genotype of MTHFR (Maristella *et al.*, 2007).

In the current study, results revealed positive correlations between homocysteine levels and BMI, insulin levels and HOMA-IR. Similarly, Gideon *et al.* (2007) also reported that homocysteine levels were higher in metabolic syndrome patients compared to patients without metabolic syndrome. But contrary to, the results of a study by Tanrikulu- Kilic *et al.* (2006) who reported that plasma homocysteine concentration was not related to insulin resistant.

Conclusion:

The study results revealed correlations between homocysteine plasma levels and BMI and HOMA-IR,

as well as with LH/FSH and testosterone level. This suggests that the interaction of high homocysteine level, insulin resistance and hyperandrogenemia may create a state mimicking polycystic ovarian syndrome that could be responsible for infertile state of these patients.

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