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EVALUATION OF HYPERINSULINEMIA, INFLAMMATION AND LIPID PROFILE IN PATIENTS WITH ENDOMETRIAL CANCER

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ABSTRACT

Endometrial cancer is the most common gynecologic cancer in developed countries and with increasing prevalence in developing countries like India. It has been hypothesized that free circulating insulin levels, Inflammation and altered lipid profile may contribute in the pathogenesis of endometrial cancer. The aim of our present study is to evaluate the role of Insulin, CRP and lipid profile in endometrial cancer. We tried to assess Insulin, Insulin resistance, CRP Levels by CLIA, Homa Index and latex agglutination method respectively. Glucose, total cholesterol and Triacylglycerol were estimated by enzymatic methods with the help of autoanalyser. HDL was measured with the help of divalent cation precipitation method.LDL was calculated by using a standard formula. For this, we have taken 25 cases of endometrial cancer cases and compared with 25 normal women who acted as controls.A significant increase in the levels of free circulating insulin, insulin resistance, CRP and triglyceride levels were observed in cases when compared with controls. A significant decrease in the levels of HDL was observed in cases when compared with controls. There were no significant differences in the levels of LDLand total cholesterol.This suggests that hyperinsulinemia, chronic inflammation and altered lipid profile may play a role in development of endometrial cancer.

KEYWORDS: Endometrial cancer, Hyperinsulinemia, C-Reactive protein, HDL cholesterol and Triglycerides(TAG).

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INTRODUCTION

Endometrial cancer is a type of malignancy that arise from the endometrium, or lining, of the uterus. Endometrial cancers are the most common Gynecologic cancers in developed countries with over 150,000 women diagnosed each year making the fifth most common cancer in women[1]. It is the third most common cause of Gynecologic cancer death behind ovarian and cervical cancer. Epidemiological studies indicate that estrogens, both endogenous and exogenous, have a major role in endometrial carcinogenesis[2,3,4]. Obesity, as measured by an elevated BMI is also a consistent risk factor for endometrial cancer[2].Obese women have higher levels of estradiol, non- protein bound estradiol, and estrone than do women of normal weight[5], and this has been considered to be the major reason for the excess risk of endometrial cancer due to obesity[6]. The other risk factors for endometrial cancer include diabetes, hypertension, PCOD, nulliparity, infertility, endometrial polyps and estrogen replacement therapy[1] etc. Insulin resistance and hyperinsulinemia may play an important role in pathophysiology of endometrial cancer. Hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis[7] and that hyperinsulinemia and insulin resistance are associated with a more aggressive course of endometrial cancer[8]. Obesity and physical inactivity, the major risk factors for endometrial cancer are the major modifiable determinants of insulin resistance, hyperinsulinemia and diabetes. Endometrial cancer is accompanied by a low grade chronic inflammation as it was found that excess body weight is associated with a systemic low grade inflammatory condition[9] characterized by elevations in circulating pro inflammatory cytokines and acute phase proteins[10]. C-reactive protein is an acute phase protein produced by the liver in response to tissue damage and inflammation. The major stimulus of CRP synthesis is interleukin 6.Inflammatory process also play a central role in the regulation of endometrial mucosa growth and shedding during the menstrual cycle[11] as well as in endometrial repair following menstruation[12].

Serum lipids may play a role in endometrial carcinogenesis. A few studies have reported an association between endometrial cancer and the risk of metabolic syndrome[13,14], including the pattern of dyslipidemia, hyper low density lipoprotein(LDL)cholesterolemia, hypertriglyceridemia or hypo high density lipoprotein(HDL) cholesterolemia. The LDL cholesterol(LDL-C)/ HDL cholesterol(HDL-C) ratio may represent the effects of both LDL-C and HDL-C. The LDL-C/HDL-C ratio has been reported to correlate with ischemic heart disease[15], but the patterns of dyslipidemia associated with endometrial cancer are not well understood. The interrelationship between insulin resistance, hs-CRP and dyslipidemia was extensively studied in multiple disorders like diabetes mellitus, chronic renal failure and metabolic syndrome etc. Studies demonstrating the relation of insulin resistance with inflammatory status and serum lipid levels in endometrial cancer were not done much in Indian population. In view of this our aim in present study is to explore the relationship between CRP and dyslipidemia with insulin resistance in women with endometrial cancer and compare it with normal healthy controls.

MATERIALS AND METHODS

The present study was conducted in the department of Biochemistry, Saveetha medical college, Chennai. After obtaining approval from Institutional Ethical Committee, 25 women with endometrial cancer and 25 normal healthy women of age group 40-70 years were enrolled. Detailed history, clinical examination and obstetric examination of cases and controls

enrolled in this study are carried out regarding any current or past history of diabetes, hypertension, systemic diseases, any other chronic physical disability and any other obstetrical complications. Informed consent from the cases and controls were taken. 5ml of fasting blood samples were collected from the cases and controls. For separation of serum, blood taken into a a plain vial is first allowed to clot and then centrifuged at 3000rpm for 5 minutes. This separated serum was used to estimate hs-CRP and lipid profile immediately and the rest of the sample was stored at -20▪C for insulin assay. The following biochemical parameters were estimated in patients with endometrial cancer and compared to controls. Serum total cholesterol was measured by cholesterol oxidase-peroxidase method and triacylglycerol(TAG) level was measured by glycerol kinase-peroxidase method. HDL- Cholesterol was measured by divalent cation precipitation method. LDL – Cholesterol was calculated using Friedwald's equation[16]. Glucose was measured by glucose oxidase-peroxidase method. All these parameters were analysed using reagent kits adapted to automated chemistry analyser Hitachi, Rosche Diagnostics. hs-CRP was quantified by latex(slide) agglutination process and serum Insulin was measured by solid phase competitive chemiluminescent enzyme immune assay using the reagents of Siemens health care diagnostics,USA adapted to Immulite-1000 Automated Chemiluminescent Analyser. Homeostasis model assessment(HOMA) index was calculated [fasting glucose(mmol/L)×fasting insulin/22.5] to assess insulin resistance[17]. All parameters were expressed as mean±standard deviation. Unpaired student 't' test was used to compare the significance between controls and cases. A "p'value of less than 0.05 was considered as significant for all statistical tests.

RESULTS

Table 1
Comparison of glucose, fasting insulin, insulin resistance, CRP levels in endometrial cancer cases with controls

Parameter	Cases(n=25) Mean±SD	Controls(n=25) Mean±SD	p value
Fasting glucose (mg/dl)	84.31±12.16	80.95±14.34	>0.05
Fasting insulin (m IU/ Lit)	14.6±2.41	6.43±1.23	<0.001
HOMA –IR	2.78±0.86	1.47±0.32	<0.05
CRP (mg/dl)	2.39±0.4	1.1±0.2	<0.05

Table 1 displays the results of serum fasting glucose, fasting insulin, HOMA-IR and hs-CRP levels among endometrial cancer subjects and healthy controls. Serum fasting insulin, 18.32insulin resistance(HOMA-IR) and CRP levels were significantly higher in cases when compared with controls. Fasting glucose was increased in cases compared to controls but not statistically significant.

Table 2
Comparsion of lipid profile in cases compared with controls

Parameter	Cases (n=25) Mean±SD	Controls(n=25) Mean±SD	p value
Serum triglycerides (mg/dl)	193.72±9.33	154.13±5.82	<0.001
Serum total cholesterol(mg/dl)	179.29±19.29	178.54±18.32	>0.05
Serum LDL cholesterol(mg/dl)	88.81±18.96	90.30±16.34	>0.05
Serum HDL cholesterol(mg/dl)	31.23±2.01	46.12±3.15	<0.05

Table 2 displays the results of lipid profile among endometrial cancer subjects and healthy controls. Serum triglycerides was significantly higher and serum HDL cholesterol was significantly lower in cases when compared with controls. There was no statistical significant difference in the levels of total cholesterol and LDL cholesterol in cases when compared with controls.

DISCUSSION

In our present study we observed a significant increase in the levels of insulin in cases when compared with controls and cases also showed increase in insulin resistance compared to endometrial cancer patients. Several epidemiologic studies have sought to evaluate the relation between elevated levels of circulating insulin and endometrial cancer risk[18,19]. Hyperinsulinemia is a hallmark of diabetes, obesity, and physical inactivity, and insulin has been shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors on endometrial cells[20]. Insulin acts to increase unopposed estrogen levels. In postmenopausal women, the ovaries no longer produce significant amounts of estrogen or progesterone, and most estrogen is produced through aromatization of androstenedione to estrone in adipose tissue[21].Hyperinsulinemia may also increase levels of free estrogens through decreasing concentrations of circulating sex hormone binding globulin[22].Estrogens in turn have been shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells[23] when unopposed by progesterone especially in postmenopausal women[24,25]. Finally, hyperinsulinemia through decreasing levels of insulin-like growth factor(IGF)-binding protein-1 and IGF- binding protein-3 increases circulating free IGF-1, which by binding and activating IGF-1 receptors in the endometrium stimulates cell proliferation[26,19]. Insulin act directly on endometrial tissue as a mitogenic and anti-apoptoic growth factor[20]. In our study we also observed a significant increase in the levels of triglycerides and significant decrease in the levels of HDL-cholesterol in cases when compared with controls. Hypertriglyceredemia is a marker of metabolic syndrome , initially defined as a risk factor for cardiovascular disorders, has recently been associated with various cancers [13,27].A case control study nested within the European Prospective Investigation into Cancer and Nutrition on 284 women with Endometrial cancer showed that the presence of metabolic syndrome was associated with endometrial cancer risk(relative risk ¼ 2.12,95% confidence interval: 1.51-2.97), and there was a positive trend in risk with an increasing number of metabolic syndrome components[28] . These findings suggest that metabolic abnormalities may act to increase endometrial cancer risk, but data on dyslipidemia with details on each type of serum lipid are limited[29]. Some researchers [29] examined the association of serum total cholesterol levels, LDL-C, non-HDL and HDL-C with endometrial cancer risk in 100

endometrial cancer cases. The results showed a positive correlation between serum triglyceride levels and endometrial cancer risk and no association between total cholesterol, LDL-C or HDL-C. Our findings were correlating with some researchers [28] who reported that triglyceride and HDL-C levels were positively and negatively associated with endometrial cancer risk respectively but total cholesterol and LDL-C were not.. Low serum HDL-Cholesterol was associated with increased free estradiol levels but unchanged progesterone levels, thus reflecting increased exposure to unopposed estrogens that is a major etiologic determinant of endometrial cancer[30]Endogenous sex steroid hormones, particularly androgens, regulate HDL-Cholesterol and other lipid levels through their action on hepatic triglyceride lipase activity and Lipolysis[31]. Other than the association of dyslipidemia with cancer, it may cause death due to cerebrovascular or cardiovascular disease.

Our study also showed a significant elevation of CRP in cases when compared with controls. It has been proposed that adiposity related factors such as cytokines and adipokines might contribute to endometrial cancer initiation and progression and to the obesity related increase in risk[32]. Chronic inflammation promotes angiogenesis, sustains cell proliferation, and increases production of free radicals that cause DNA damage, leading to tumor initiation and development [33]. Inflammatory processes also plays a central role in the regulation of endometrial mucosa growth and shedding during the menstrual cycle [11] as well as in endometrial repair following menstruation [12].Interleukin 6 which is the major stimulus of CRP synthesis is responsible for the recruitment of monocytes during chronic inflammation and therefore plays an important role in the transition from acute to chronic inflammation [34]. Another mechanism for the inflammation mediated association with endometrial cancer could be the modulation of aromatase activity by cytokines within the adipose tissue[35] . After menopause, when the estrogen production from the ovary has ceased, most of the circulating estrogens derive from the peripheral aromatase conversion of androgens in the adipose tissue. It has been shown that IL6 can stimulate aromatase activity in the adipose tissue [36] and therefore enhance the estrogen production and bioavailability. Furthermore, inflammatory markers have also been shown to play an important role in the development of insulin resistance, hyperglycemia and type-2 diabetes [37] which are known risk factors for endometrial cancer [32.] The levels of hsCRP was a significant predictor of risk even in the subgroup of women with LDL-C levels below 130mg/dl [38.]

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